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Specific constitutional treatment of cancer

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THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

A REVIEW

by

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PREFACE

The physician and medical student may have heard mention of constitutional methods of treatment of cancer. Such methods are seldom referred to in textbooks or classrooms, but are occasionally presented at medical meetings, especially those primarily interested in the study of malignant disease. The infrequent and sometimes casual references made to the subject will fail to impress one of its scope, and of the immense amount of work which has been done in an attempt to find a <u>therapia magna sterilisans</u> for cancer. Furthermore, one who presents positive findings is apt to omit reference to numerous studies which have yielded negative results and thus leave his audience with a distorted outlook on the subject. It is, therefore, to orient the student to this field of cancer research, to survey a large group of methods and substances proposed for the specific constitutional treatment of cancer, and to reach some conclusions as to their value, potential and attained, that this paper is written.

THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

CONTENTS

THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

I

INTRODUCTION

SCOPE.--This paper is a review of the treatment of cancer by substances and methods which are introduced into the body distal to the tumor and which exert a specific deleterious action, directly or indirectly, upon the cancer cell, resulting in regression of the tumor and cure of the affected patient. Included are chemicals, gland and tissue extracts, bacteria and their growth products, body fluids, toxins, and a number of physical methods. While certain immunologic methods are of this general nature, they are not included here because of some rather fundamental differences in the problems involved and because the subject is so voluminous as to merit a special study of its own. It has recently been thoroughly reviewed by Woglom (1929) and Caspari (1929). Obviously excluded from consideration by the stated scope of this paper are methods of prevention of cancer, treatment by dietary restrictions, and treatment by removal of organs of internal secretion. Numerous publications have, from time to time, accepted a method of constitutional treatment which was a current favorite and described it without citing observations regarding its value, but as this is written with some view to estimating the value

of proposed methods, such publications are not considered here. Quacks have often employed constitutional methods to treat cancer patients but are deserving of no consideration.

GENERAL CONSIDERATIONS OF CANCER BEARING ON TREATMENT.--A tumor is defined by Ewing (1922) as an autonomous new growth of tissue. Such growths subserve no useful function and are largely uncontrolled by the organism. Tumors are divided into benign tumors and malignant tumors or cancers. The latter group consists of those tumors which exhibit certain features which are essentially deleterious to the host, most important of which are infiltrative growth, local destruction of tissue, recurrence after removal, formation of metastases, local interference with function, and general toxic action of absorbed tumor products.

There are numerous theories as to the cause or causes of cancer, but no general single cause has as yet been proven. The following theories are particularly well known: the embryonal rest theory of Cohnheim, the tissue tension theory of Ribbert, the theory of tissue growth of Adami, irritation, heredity, metabolic derrangement, and specific parasite. Most of the theories are not entirely satisfactory because the postulated cause cannot be shown to operate in a majority of the cases of cancer and because the cause can be present without

resulting in cancer. Often a supposed cause has later been shown to be only a phenomenon which is part of the cancer process itself or which is secondary to the neoplasm. It has become necessary, therefore, to suppose a multiplicity of factors to be involved, varying in different cases,--some are exciting and some are predisposing, some are general and some are local, some acquired, some hereditary. If cancer is a parasitic disease (there is much evidence to show that it is not), it is important from the point of view of treatment to determine whether the continued presence of the parasite is necessary for the continued growth of the malignant cells once the process has been initiated (Boyd, 1925).

Regardless of the cause of cancer, it is generally accepted that the process is itself specific, the growing cancer cells constituting, as it were, an invading "organism". The cells are specific in their property of unlimited and unrestricted growth as a result of perversion of normal functional and nutritive relations. The energy for excessive growth is liberated by abnormally excessive carbohydrate cleavage (Warburg, 1931). Other properties of cancer cells are atypical structure, increased permiability, abnormal lipid relations, electrical reactions, response to calcium salts and intracellular water content, and excessive co-ferment primary in the cleavage of dextrose (Eggers, 1932). Factors contributing to the

increased reproductive capacity are inherent growth energy, heredity, hormonal imbalance, and, probably of greatest importance, factors as yet unknown.

The well known property of cancer to invade and metastasize, which often renders local treatment incomplete, makes a specific constitutional method of treatment desirable. With all treatment at the present time consisting of local excision or destruction, the best medical skill attains only about fifteen percent of definitive cures for all types of cancer (Haagensen, 1933). Failures result from incomplete removal. While the percentage of cures will undoubtedly be improved by earlier diagnosis and improved technique, it can never approach the results to be attained with a successful constitutional form of treatment. The importance of this field, therefore, lies in the treatment of cases advanced beyond the hope of successful surgery or irradiation and in prophylaxis against recurrence following excision or destruction.

At present, there is no method proven successful in any high percentage of cases. The methods attempted, however, will be reviewed and their results evaluated.

SPECIFIC CONSTITUTIONAL TREATMENT.--A large number of the methods reviewed here may be classed as chemotherapeutic. Some of the specific constitutional methods, however, such as the use of hormones and bacterial growth products,

could only questionably be called chemotherapeutic, while others, such as fever therapy, in no sense fall into this realm. The attempt is to review all methods not specifically excluded.

Chemotherapy, as stated, does play a large part in the specific constitutional treatment of cancer. Barger (1930) defines chemotherapy as the use of drugs on which chemical work has been done, usually synthetic substances, alkaloids or their derivatives, in the treatment of parasitic disease, acting by its toxic effect on the specific causative agent. Kolmer (1926), however, states that in the modern sense chemotherapy includes the treatment of parasitic disease by more or less specific disinfection of the tissues without marked or serious toxic effect on the host. The chemotherapeutic agent need not necessarily be monoparasitotropic and it may act indirectly by production of leukocytosis, stimulation of phagocytosis of other immune defense as well as directly upon the parasite. He discusses such fundamental conceptions as parasitotropism and organotropism, chemotherapeutic index, leads and chemoreceptors.

Kolmer (1926) considers the use of chemotherapy in cancer as dependent upon the etiology of cancer: (1) if due to a change in cells resulting from prolonged irritation, a substance which will destroy the cells produced must be found; (2) if due to specific virus

alone, discover a specific destructive chemical agent for it; (3) if due to chemical irritation, chemotherapy could not remove it; (4) if due to irritation produced by a specific or non-specific organism, the chemotherapeutic substance would have to destroy the organism causing the irritation and the cells already changed. Findlay (1930) regards the cancer cells as specific; any chemotherapeutic method must destroy all the cancer cells by its direct lethal action upon the malignant cells, by destruction of the blood vessels to the tumor, or by stimulation of defensive and fixed tissue cells. The first of these possibilities, direct destruction of the tumor cells, is ideal, but very difficult because of the great similarity of cancer cells to normal cells. The metabolic difference detected by Warburg is suggested as an important basis for rational therapy.

GENERAL CONSIDERATION OF THE METHODS.--The many substances and methods which have been proposed for the specific constitutional treatment of cancer may be classified as follows: (1) metals and metallic compounds; (2) other inorganic compounds; (3) other organic compounds; (4) a miscellaneous group of substances including hormones and tissue extracts, bacteria and their growth products, toxins, and body fluids; and (5) physical methods,--fever therapy, gas inhalation, and modification of fluid balance.

The usual dose of the substance employed is

sufficiently large that its toxicity is of great importance, although a few are used in relatively non-toxic doses. Since highly toxic doses of substances are dangerous, their use is impractical and they are without value. Every known method of administration has been used, but since the effect of intratumoral injection may not be constitutional, reports of such treatment are not included.

Subjects for the investigation of proposed remedies have been animals bearing various types of experimental cancer and human inoperable cancer. Objection has frequently been raised to reports based upon the use of one type only of animal tumor and to the use of transplantable tumors. Provided the experiments are properly controlled and the animal work is used only to get leads as to possible value in treatment of human cases, no valid objection can be raised.

The substances and methods used have produced a great variety of local and general effects. Some observers have gone to great lengths to describe in minute detail these changes. For our purposes, such descriptions serve only to cloud the true results, for we are interested here only in destruction of the cancer and cure of the victim. Because of the results of their experiments, most observers reach some conclusions as to the value of their form of treatment. These are given where they have been made and discussed later in the

light of certain criteria.

Weil, who was one of the early workers in the field of chemotherapy in cancer, sought some basis for evaluation of the results of his experiments and those of others. He concluded (1913) that "the demonstrable reduction in size of a tumor, of a kind not to be attributed to the natural processes of evolution of that tumor or of its associated lesions, is the one essential feature of effective therapeutic intervention." By way of explanation and expansion, it may be stated that this refers to established, proven malignant tumors, that they must be reduced in size and metastases must not develop, and that the natural process of evolution of the tumor and its associated lesions must be noted in untreated controls and conclusions based upon differences in the two series. Furthermore, that the remedy may be considered specific, it must be effective in a significant percentage of the cases treated. In human cases, the percentage of five year cures computed according to the rules laid down by the cancer commission of the health organization of the League of Nations (1929) constitutes a second necessary criterion for the evaluation of the results of treatment. The above are reasonable and necessary yardsticks, yet the majority of investigators in this field are unaware of the necessity of basing their conclusions on these or any other guides.

THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

II

HISTORY

CANCER.--The history of our knowledge of cancer is divided by Ewing (1922) into four periods. The first of these began in the earliest times and lasted until about 1661. The earliest medical documents, the Papyrus Ebers, about 1500 B. C., refers to tumors in general, but there is no clear reference to cancer. Lipoma is clearly described,--it is treated "with the knife". Hippocrates (460-375 B. C.) knew cancer well and described many forms. He advised against treating deep-seated lesions; only cautery and various caustic pastes were recommended. Galen (130-201 A. D.) made no significant contribution to the knowledge of either the cause or treatment of cancer; his work is important only because his authority was so great that he crystallized medical thought and obstructed progress in the investigation of cancer until after the Renaissance. The humoral pathology by which deficiency or excess of bile, blood or mucous formed the basis of all disease disseminated conceptions of the origin of cancer and prevented progress for nearly two thousand years. In his classification, Galen included many inflammatory lesions, localized edemas, gangrene, and other affec-

tions which he could not understand with true tumors. He attributed cancer to an excess of black bile. Local treatment of cancer improved somewhat, but the ideas as to the nature of the disease remained about the same until the lymph theory of Malphigi began the second period in our knowledge of cancer in 1661.

Harvey discovered the circulation of the blood in 1628; Olens discovered the lymph vessels in 1652; Malphigi discovered the red blood corpuscles in 1661. Lymph coagulated and foamed on boiling, hence cancer was composed of lymph varying in density, alkalescence or acidity. Galen's doctrine was demolished. The lymph theory dominated thought until 1852. Morgagni's work in 1761 constituted the beginning of pathology and the beginning of the description and classification of cancer. Schwann showed that all living matter was composed of cells in 1838, and Johannes Müller founded microscopic pathology at about this time, but held to the lymph theory.

It remained for Virchow in 1858 to begin the histologic period of our knowledge of cancer with his dictum "omnis cellula e cellula". Virchow believed that all malignant tumors arose heterologously from connective tissue. Thiersch corrected this in 1865 by changing Virchow's dictum to "omnis cellula e cellula ejusdem generis".

The present period in the study of cancer is the experimental period, which began with the Twentieth Century. It began with the successful transplantation of a spontaneous carcinoma of the vulva of a rat to the testis of several male rats by Hanau in 1889. Jensen carried a mouse carcinoma through nineteen generations in a classical study in 1903.

CHEMOTHERAPY.--"From the earliest times healers of the sick have sought specific remedies in the form of drugs or methods that would always and unfailingly cure the effect of a certain disease" (Kolmer, 1926). Many substances have been used and mostly discarded. At the beginning of the modern era, there were only three of proven value,--mercury for syphilis, since 1500, and cinchona bark for malaria and ipecacuanha for dysentary, since the Seventeenth Century.

Modern chemotherapy began with Ehrlich who, stimulated by Heubel on lead poisoning, idealized "that the ways and means by which drugs are distributed over the body must be of great importance in the rational development of therapeutics." His work with the arsenicals in the treatment of syphilis began the modern era of rational chemotherapy.

CHEMOTHERAPY IN CANCER.--Constitutional methods have been used in the treatment of cancer since earliest times. Cato administered charcoal and a variety of crude internal

remedies were mentioned by Pliny. Avicenna (980-1037) administered arsenic internally. Fabricius (1537-1619) experimented with various internal remedies. With the decline of Galen's authority in the Seventeenth Century, treatment was demoralized; arsenic and other internal remedies were abused. Helmont and Ettmuller thought cancer due to an excess of acid and treated it with alkali. Hoffman applied his anodyne to restore tissue tone. Goulard used a lead preparation, lead subacetate, locally in 1760. Torres first used colloidal metals in 1904 (see Waters, Colston and Gay, 1929).

The rational investigation of the application of specific constitutional methods of treatment to cancer depended primarily upon the existence of a rational chemotherapy as founded by Ehrlich. Experimental methods of cancer research, while not absolutely essential, were very desirable, and were most important for the investigation of the value of a large number of substances in the specific constitutional treatment of cancer.

The modern history of the specific constitutional treatment of cancer began with the use of killed cultures of Streptococcus erysipelas in the treatment of animals bearing spontaneous neoplasms by Spronck in 1892 and with the use of the mixed toxins of Streptococcus erysipelas and Bacillus prodigiosus in the treatment of human cases of inoperable malignancy by Coley in 1893.

The first work with chemotherapy proper was that of Wassermann, Keysser, and Wassermann, reported to the Berlin Medical Society in 1911. They treated mice that had been innoculated with transplantable tumors with an eosin-selenium compound, thinking that the eosin would carry the toxic selenium into the cancer cells. They believed that they had cured a few animals, but their preparation was soon shown to be without value. Their work, however, had attracted wide attention and others were led to similar attempts. Leob, et al, in this country, reported on the use of copper compounds in 1912.

For the most part, the subsequent history of the specific constitutional treatment of cancer is the history of the use of the individual substances and methods which have been proposed.

THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

III

METALS AND METALLIC COMPOUNDS

Metals have played a most important role in the treatment of cancer. Where they have been used, the action of the compound has been, for the most part, ascribed to the effect of the metal. Whether or not the action of the substance is in every case due to the metallic constituent, such an assumption serves as a convenient basis for classification. Caspari (1928) theorizes as to the action of all heavy metals. He believes they increase the autolytic processes of cells, all thus having a general harmful effect on tumors. The colloidal form has been believed especially useful for various reasons, probably the most valid of which is the idea that metals are less toxic in such form than in compounds in which the metal is ionized.

Before considering the individual metals, it seems desirable to discuss four papers which have each reported upon the use of a large number of metals and a few non-metals in the therapy of tumors in animals. Ishiwara (1927) investigated the effect of compounds of fifty-eight different metals upon mice bearing the Bashford carcinoma No.63. He divided these substances into four groups on the basis of their effect. All the metals

to be mentioned later with the exception of sodium, potassium and chromium were included in the tests. To test the validity of the positive results reported by Ishiwara, Simpsom and Marsh (1931) and Marsh (1934) investigated the effect of one hundred nine compounds upon albino mice bearing spontaneous mammary adenocarcinoma. They included all the metals of Ishiwara's series except praseodymium, niobium, ytterbium, and terbium (the latter three were classed as effective by Ishiwara). All the substances mentioned later in this paper except praseodymium were included in one of these papers. Not one of the one hundred nine compounds employed showed any evidence of therapy, macroscopic or microscopic, upon the tumor or its growth. All three papers include substances which are not considered later because the only reference to the use of such substances in the treatment of animal or human tumors is in these papers. The results of Maxwell and Bischoff (1931) were negative for all substances employed on the rat sarcoma No. 10 except praseodymium nitrate. With the Hyde rat carcinoma, all their results were negative.

LEAD.--Goulard introduced lead for the local treatment of cancer in 1760, but it was not until the work of W. Blair Bell in 1922 that attention was called to its possible constitutional use. Bell had observed the frequency with which spontaneous abortion occurred in

women employed in the lead industry. He reasoned that this was due to a specific harmful effect exerted by the lead upon the embryonal cells such as occur in the chorionic villi. Cancer cells resemble those of the chorionic villi in their primitive structure and invasive tendencies, and should, therefore, likewise be harmfully affected by lead. Furthermore, on the basis of the work of Bullock and Cramer (1913-14), who showed that certain transplantable tumors of the mouse and rat had a tendency to a higher content of phosphatids and cerebrosides than normal tissue and that the content was higher in rapidly growing tumors than the more slowly growing ones, Bell argued that the action of the lead consisted of a combination with the lecithin of the tumor cells. Of their numerous communications, several have dealt solely with these theoretical considerations and their experimental proof (Bell et al, 1925). Other investigators have contended, however, that lead acts on the vessels of the tumor.

Animal Tumors.--Wood (1926) used colloidal lead on a group of nine hundred white rats bearing a transplantable carcinoma and two transplantable sarcomas, all highly virulent. The tumors were greatly affected,--there was extensive necrosis in most, but all but a few recurred. A very few (number unstated) were completely absorbed. Wood believed that the lead caused thrombosis of the newly-formed, fragile vessels of the tumor. Girard (1927) found lead to be the best of a group of

metals applied by electrical endosmosis to a spindle-celled rat sarcoma, causing absorption which was sometimes complete. Vecchi (1930) used twenty-five albino rats implanted with osteoid sarcoma; there were twenty-four takes. Using nine as controls and dividing the remainder into three groups of five, he found that the treated animals had smaller tumors at every observation period over a period of forty days except the first (fifteen days). Wood (1927), in a later work, found that colloidal metallic lead combined with irradiation was more effective on the rat sarcoma No. 10 and on the Flexner-Jobling rat carcinoma than either lead or irradiation. Dextrose failed to increase the effectiveness of either the lead or irradiation. The Jensen rat sarcoma was uninfluenced by lead salts injected intramuscularly in oil (LeGuyon, 1931). Eggers (1934) treated animals inplanted with the FRC carcinoma and the R39 rat sarcoma with lead salts of acids derived from a group of hexose sugars in an attempt to utilize the metabolic peculiarity of cancer cells discovered by Warburg. While the glycuronate, galactonate and glucoheptonate were successful in a few cases, Eggers considered his results with these compounds unsatisfactory.

Mottram (1928) investigated the effect of combined lead and irradiation on mouse carcinoma T63. Tumors disappeared following combined therapy in such

doses of each as would be ineffective alone. He concluded that the action was a summation of the effects of each; also that the substances acted upon the vessels of the tumor, partly by secondary radiation, and that the results were sufficiently encouraging to warrant trial in human cases. Krause, and later Collier, have undertaken the investigation of a number of organic lead compounds in an effort to modify the toxicity of the product and maintain its therapeutic potency. Krause (1929) first reported upon the investigation of a group of such compounds on mice with experimental carcinoma. n-propyl lead flouride $(n\text{-}C_3H_7)_3PbFl$ was especially effective in the prophylaxis and treatment. Collier (1929) tested Krause's compounds on mice two hours after innoculation with the Ehrlich carcinoma. While all of three hundred controls died in four to six weeks, the treated animals frequently showed no growth whatever, or growth to a small size with later regression. Best results were with n-propyl lead flouride and tetraphenyl lead. In 1929, Collier also investigated the effect of fifteen inorganic and organic lead salts on transplantable mouse tumors, most of which inhibited growth in twenty to thirty percent of the cases. The best results were with the tannate, oxalate, malate, and citrate, and especially with the formate, which retarded nearly sixty-five percent and caused the dis-

appearance of thirty-five percent. Collier and Krause (1931) treated mice with solutions of heavy metal compounds two days after innoculation with the Ehrlich carcinoma. Most active were $K(PbCl_3)$ and $K(Pb_2Cl_5)$. Krebs and Clemmesen (1934) gave R237b (see below) to one hundred mice with Krebs 2 carcinoma, a tumor that has not yet receeded spontaneously. There was no difference in the controls and the treated animals.

Collier (1932) found the potassium salt of plumbo-dithio-pyridincarboxylic acid, called R232, to retard the growth of the Brown-Pearce rabbit carcinoma, and to prevent the development of metastases. While Krebs and Clemmesen had some success with this compound and its sodium salt (R237B) on the Brown-Pearce rabbit carcinoma and in leukoses of fowls, they found the latter of no value in a mouse tumor. While Bell published his first paper on the treatment of cases of human malignant disease in 1922, it was not until 1935 that his organization investigated the value of lead compounds in the treatment of animal tumors. At that time, a group of twenty-seven organic lead compounds were tested by the Liverpool Medical Research Organization under M. Datnow. The Brown-Pearce rabbit carcinoma was used, and of the twenty-seven compounds, seven were entirely unsuitable because of their toxicity and five had been only partially tested. Some of the others will be used in human cases.

Results following the use of manganese combined with lead phosphate on rats with sarcoma 39 lead Kraemer (1931) to advocate the use of this combination in cases of human cancer. Marsh and Simpson (1927) treated female albino house mice bearing spontaneous mammary carcinomas with lead tetra-ethyl. It had no effect except in lethal doses.

Dilling (1928) and a number of other observers have reported concentration of lead in tumors. Reinhard and Buchwald (1929) treated mice bearing spontaneous mammary carcinomas of various duration with varied doses of lead colloid. They examined theytumors spectroscopically and by two chemical methods and could find no lead whatever in the tumors.

Human.--Bell employed various preparations of colloidal metallic lead. A colloidal preparation was used because it was thought to be less toxic than other compounds. His first paper (1922) set forth the theoretical considerations upon which the work was based and gave the results of his early clinical experiments. Inoperable cases were selected and, while none were refused, it was thought that the patient should be able to live six months without treatment to be a good risk. Lead was found in the tumors in considerably greater concentration than in the other tissues and was thought to increase the sensitivity to irradiation. As much of

the growth as possible should be excised to prevent toxic absorption and to reduce the amount of treatment necessary. Fifty cases were treated over a two year period and four of the thirty-five receiving a complete course of treatment were considered cured. Two of these had been treated with lead alone and two had combined irradiation and lead therapy. Reports on the progress of his work were made by Bell and his co-workers in 1924, 1925 and 1929. The 1929 report, which is the last one made (Bell died early in 1936), includes a total of 566 cases, treated over an eight year period ending in November, 1928. Of these, 450 died; 22 discontinued treatment; 12 were completely arrested; 51 were believed cured and treatment stopped; and 31 were recent cases. Thus, of the 315 having adequate treatment, 63, or twenty percent, had satisfactory results. Slightly over ten percent of the whole series had satisfactory results.

Following the work of Bell, Stone and Craver (1927) treated six cases successfully with colloidal lead out of a total of twenty-one. Four were primary bone tumors. A case of chorioepithelioma was unaffected. Wood (1928) treated forty patients who had inoperable or recurrent malignancy. Four were living and well after a year with no sign of neoplasm, and the tumors had completely disappeared in two others that died of inter-

current disease. Colloidal metallic lead and irradiation were used. Hume (1928) treated thirteen cases with Bell's preparation S7 alone with no improvements, but noted improvement in two of seven cases in which irradiation was combined with the lead. Soiland, Costalow, and Meland (1928) treated a series of eighteen cases and arrested one case of carcinoma of the cervix which had previously been treated with radium for an unspecified length of time. Knox (1929) treated forty patients, of which four were well and wholly free of all signs of cancer at the end of a short period of observation. Brunner (1929) reported definite improvement of an unstated nature in seven of fifteen patients. Brunton (1930) completed the treatment of thirty-four patients with S7. There were two clinical cures of a duration of three years.

O'Crowley (1926) treated two cases of epithelioma of the penis with colloidal metallic lead. They were unaffected. Talbot (1928) failed to cure two cases of cancer but thinks their lives prolonged. Hey (1928) noted no effect on twenty cases. Eight cases of Kaemmerer (1928) received adequate dosage without being in any way improved. Wyard (1928) reported on fifty-six cases treated at the Cancer Hospital, London, with one good result in an unproven lymph node recurrence of a cancer of the breast. From his own observations, he concluded

that lead is of no use in the treatment of cancer, and from other reports available at the time, he concluded that there was no reason why lead should be of use and no evidence that it is. All of the seventeen cases treated by Schreiner and Wende (1929) died or metastases occurred. The results of Mattina (1930) on twenty cases were similar. Dalimier and Schwartz (1934) treated seven cases with a colliodal metallic lead preparation and seventeen cases with lead phenylamylacetate. The end results in these cases were unchanged, and the authors concluded that the treatment had been without value.

Colloidal lead phosphate has had considerable vogue in treating malignant disease. Ullmann (1928) reported two cases greatly improved out of a series of cases treated. In a later report (1929) on fifty-seven cases, five had responded favorably and five were too recent for evaluation. Osterberg, Horton, Bargen, and Rankin (1932) treated ninety-five cases with colloidal lead phosphate at the Mayo Clinic. Of the forty-eight cases receiving what the authors considered adequate treatment, twenty-six died and twenty-two were living at the time of the writing, six months to two and one half years after beginning treatment. Nine were clinically free of all signs of neoplasm. In a later series of eighty-one cases treated, for the most part, with combined lead and irradiation (1935), sixty are known dead,

seven are either not traced or are known to have recurrences, and thirteen are living and clinically well after at least two years. Of the latter group, seven received lead alone and six received lead and irradiation. Thus, about sixteen percent were successfully treated. Aub and Smithwick (1933), however, treated twelve patients who were in relatively good condition despite the presence of an inoperable neoplasm, using combined lead and irradiation, and not only failed to attain any successful results but felt that the patients were made worse and their duration of life shortened by the treatment. Soiland, Costolow and Meland (1929) likewise failed to cure any of thirty-one cases with the combined treatment.

Other lead preparations have been used, and some have tried several lead preparations, or lead and some other substance, in a series of cases. Thomson (1928) used colloidal lead (choriotrope), lead glycine and lead phosphate in a group of fifty-five cases. Six were too recent for evaluation, while only five were improved. Coke and Cook (1926) experimented with several lead compounds and apparently cured one case with lead and X-ray. Dentici, Moratti and Pattarin (1929) treated twenty-five cases with a lead preparation. Two which had not been biopsied completely regressed, three partially regressed, sixteen died, and seven had not completed the treatment. Waters, Colston and Gay (1929) had poor

results with two series of cases in which a lead compound had been combined with irradiation. Costa (1930) treated seven cases with lead "Dezani", a proprietary preparation, with no cures. Schlurch (1933) treated thirty-two cases of inoperable carcinoma with lead iodide in calcium gluconate solution and noted no objective improvement attributable to the lead in any case. Simpson (1928) treated nineteen cases with a lead preparation. Eighteen died and the other one was unimproved. Colloidal lead oxide was used by Loewy and Loiseleur (1928) in the treatment of twenty-one cases. Localization of the lead in the tumor was noted and arrest of development of the tumor was thought to occur in four cases. A later report, however, failed to confirm the early favorable results (1928). Fry (1928) found no histological changes in growths treated with lead not observed in untreated tumors.

Todd and his associates (1928) worked with compounds of lead and selenium, based on previous claims of value in each. Their first report on forty-four cases treated with colloidal lead selenide (D4S) recorded no cures, but retardation of growth occurred in eight cases and twenty-five died. They warned against the use of this substance combined with irradiation (1929). In 1930, Todd reported on the progress of his work, and in 1934 the last available report was made. He believes that the treatment stimulates the natural body defense against

invasion by the cancer cells. The original preparation, D4S had proven unsuccessful and the use of it discontinued in favor of selenium preparations containing no lead.

COPPER.--Copper compounds were among the first substances to be widely tried experimentally for the chemotherapy of cancer. Loeb began its use in this country in 1912, while a group of observers were favorably impressed in Europe.

Animal Tumors.--Loeb (1913) used a group of preparations of colloidal metallic copper in mixture with casein and claimed to have cured a few mice bearing a transplantable adenocarcinoma. Next, a group of substances,,including platinum, sulfur, lanthanum, and ethylhydrocuprein, were tried in combination with colloidal copper (Loeb and Fleisher, 1913). All were ineffective. Of a group of proteins, casein and nucleoprotein alone were effective, but no cures resulted. Finally, colloidal copper and colloidal copper combined with casein or hirudin were found to inhibit the growth of nine to thirteen day old mouse carcinomas, being more effective in smaller, more rapidly growing tumors than in larger, more slowly growing ones, these results being reported by Fleisher and Leob in 1914. Neuberg, Caspari and Lohe (1912) were unable to find tumor cells in mice cured by a copper preparation of spontaneous and transplantable tumors. Their later work failed to confirm these good

results. These authors proposed the theory that since, according to Petri, tumor cells had increased quantities of autolytic ferments, and according to Izar, colloidal metals increase the activity of autolytic ferments, therefore, the colloidal metals affected cancer cells by enhancing autolysis. This theory has never been confirmed. Szecsi (1912) was unable to attain satisfactory results with colloidal copper. Keysser (1914) found that while the colloidal copper glycine of Neuberg cured some cases of subcutaneous innoculated tumors of mice, it was of no value whatever in infiltrating tumors and metastases of organs. Cells of a transplantable tumor suspended in it in vitro grew when implanted into new hosts.

Human.--Loeb et al (1912) began the use of colloidal copper in cases of human cancer in May, 1912. Their report, made in December, as well as one made early the following year, on nineteen cases treated with colloidal copper, noted improvement in most cases, especially those of slow growing tumors without too extensive metastases. No cures were claimed. McClurg, Sweek, Lyon, Fleisher, and Loeb (1915) treated a group of cases of non-keratizing cylindrical-celled cancer of the skin and a group of cases of squamous-celled cancer with their copper-casein preparation. Detailed case reports were given, but no cures of cases of proven malignancy were claimed. Weil (1913) treated twelve cases of cancer with colloidal copper,

eight of which completed the treatment; he stated that every improvement except destruction of the tumor occurred, and concluded that it is of no value in any case. Soiland, Costolow and Meland (1927) noted no effect in four cases treated by intramuscular injections of colloidal copper.

SILVER.--Animal Tumors.--Neuberg, Caspari, and Lohe (1912) found colloidal silver to be especially valuable in treatment of transplantable and spontaneous tumors of mice. Silver preparations were marketed under the names of fulmargin and electrargol. Rohdenberg (1915) used colloidal silver and lecithin in phenol solution to treat mice with the Ehrlich carcinoma. His experiments were controlled with mice that were untreated as well as by those treated with silver and lecithin alone. One series showed slight benefit to all those treated over the untreated animals; variation in the percentage of the constituents had no effect. Treatment had no effect whatever, however, on animals bearing the Crocker Fund mouse carcinoma No. 5. Walburn (1930) treated 130 mice bearing tar tumors with dilute solutions of silver nitrate. There were fourteen complete regressions.

Human.--No favorable results have been reported in the treatment of human cancer with silver preparations. Rohdenburg (1915) treated ten cases with colloidal silver and lecithin, all of which had had tissue diagnosis. All

the patients died. Stone, Pack and Woodard (1930) used a preparation of colloidal silver prepared similarly to colloidal lead. There was no alteration in the course of the disease in the patients treated.

BISMUTH.--Animal Tumors.--Zadik (1930) claimed successful results in the treatment of a transplantable sarcoma of the rat with a bismuth preparation, Bismuth Yatren A, combined with isamine blue. Ishiwara (1927) found bismuth ammonium tartrate to be the only one of twenty metallic compounds successful in inhibiting the growth of the Flexner rat carcinoma.

Human.--The success of Zadik in treating human cases with his mixture was reported at first as being only temporary. In a later report (1930) on the treatment of 109 cases with isamine blue and bismuth (Wismut Yatren A, an organic acid containing bismuth and iodine), he claimed definite improvement in thirteen cases observed up to two years. Kahn and Wirth (1927) treated ten cases with colloidal bismuth (Wismut-Diasporal 360), in solution with dextrose, and X-ray. Their report at the end of a year claimed some beneficial results. Lasch and Neumann (1929) treated eighteen cases by Kahn's method, and noted an effect only in those cases in which X-ray was also used, but even here the results were poor.

MAGNESIUM.--Animal Tumors.--Delbet and Pallios (1928) claimed that transplantable tumors in an unstated number of mice

were retarded in growth by oral and subcutaneous administration of magnesium compounds. Bolaffi (1930) treated rats bearing an adenocarcinoma with magnesium chloride subcutaneously and orally and found only very slight prolongation of life as compared with controls and reduction of the size of the tumor in only certain instances. The magnesium content of the tumors was not altered, but the calcium to potassium ratio was increased in some instances. A later report (1930) on the use of magnesium iodide and magnesium phosphate combined, or the latter alone, concluded that magnesium has no inhibitory effect on the growth of carcinoma of the rat and is of no value in treatment. Shear (1933) made an extensive review of the literature and carried on numerous experiments of his own in a study of the role of magnesium in cancer, approaching the problem from the standpoint of the content of the blood and the tumor of magnesium and the effect of its use in treatment. He concluded that there is some question as to its value in the treatment of cancer but that the retarding effect claimed for it certainly does not exist, and that no points are sufficiently established to warrant clinical trial. Sugiura and Benedict (1935) studied the influence of magnesium on the growth of carcinoma, sarcoma, and melanoma in animals. They found that administration of very low magnesium diets to animals after growth of transplantable tumors became established had

no marked inhibitory effect on the tumors, that very high magnesium diets slightly accelerated growth of tumors but that more regressions occurred, and that prolonged use of a high magnesium diet in animals with established Flexner-Jobling rat carcinomas, mouse sarcoma 180 and the Passey mouse melanoma did not check the growth of the tumors.

Human.--Schrumpf-Pierron (1931) believed that lack of intake of sufficient magnesium to be a cause of cancer. He attempted to show that cancer is about ten times as frequent in Europe as in Egypt and held that this is due to the fact that the soil of Egypt contains fifteen to seventeen times as much magnesium as that of France. Ernst (1932), however, was unable to report any cures among fifty-four patients treated by irradiation and a complex preparation containing magnesium. Craig (1934) used magnesium chloride with apparently good results in one case of carcinoma of the larynx observed over a period of only a few months. Cure was not claimed. Wright (1934) reported on four cases treated with magnesium sulfate; benefit was thought to have resulted from the treatment but no cure was claimed.

GOLD.--Animal Tumors.--Lewin (1913) used colloidal gold, gold potassium cyanate and other gold salts in the treatment of animals with malignant growths. There was some effect, which Lewin attributed to action on the young

capillaries of tumors, which he thought particularly easily injured. Fleisher and Loeb (1914) treated mice with carcinoma with colloidal gold and gold potassium cyanate, with little effect.

Human.--Ochsner (1926) reported very favorably on the use of pure colloidal gold suspended in pure water in the treatment of cases of inoperable cancer. He gave case reports on five cases, one of which was alive and well after an interval of about four years. He sent questionaires to 182 physicians who had treated a total of 309 cases with colloidal gold. Six were reported cured and ninety-seven were too recent for opinion. Thus, out of 212 cases having sufficient treatment, six, or about three percent, were claimed cured. Soiland, Costolow and Meland (1927) treated an unstated number of cases of inoperable cancer with colloidal gold by mouth with no effect.

ANTIMONY.--There have been no reports on the use of this metal in animal tumors, but Minervini (1928) reported on the use of a combination of antimony tartrate and extract of ipecac root given by vein and intratumorally in cases of inoperable human cancer. At the time, he gave no results, but a later communication (1929) described the results in 141 cases of carcinoma and fourteen cases of sarcoma, all proven histologically. The preparation used was a solution of all the alkaloids of ipecacuanha with the addition of anitmony potassium tartrate, a preparation he called Antiblastoma L. He discouraged the use of irradiation with this treatment. He claimed that

in about one third of the cases arrest of the growth with decrease in size and sclerotization occurs. He has observed cases up to two years. Cestaro (1930) used Antiblastoma L in two cases and claimed one and two year cures. Pattarim (1931) found Minervini's preparation to be of no value in any of twenty cases.

RADIOACTIVE ELEMENTS.--Animal Tumors.--Spies (1931) treated mice innoculated with the Twort carcinoma with uranium nitrate and thorium nitrate. The tumors grew faster in the forty treated animals than in the forty controls, due, Spies thought, to the stimulating effect of radioactive substances. Burrows (1934) treated rats bearing the Jensen sarcoma with a diverse group of substances, including thorium, gelatin, and alum. A higher percentage of retrogressions occurred in those treated by any method than in the untreated animals. The author believes this due to the fact that many things affect the host and result in reduced vigor of tumor growth, yet have no therapeutic value. He points out that conclusions based on the weight of the tumor are fallacious, as well as those based solely upon grafted tumors. He considers good results with the more reliable grafted tumors, such as the Crocker Fund mouse sarcoma 180, an indication for later use on spontaneous tumors before trying on human cases.

Human.--Hocking (1928) used the feebly radioactive substances uranium and thorium in an effort to combine the local effect of radium and the general effect

of lead and yet avoid the purely local action of radium and the toxic effect of lead. He treated thirty-one cases with these substances in colloidal solution and claimed improvement in seventy percent. One case of cancer of the breast with metastases is alive and well after twelve months. Pack and Stewart (1930) treated eight cases with Hocking's preparation in an effort to check his results. One was slightly benefitted but his life not prolonged, while the other seven were not benefitted in any way.

MISCELLANEOUS METALS.--A number of metallic preparations enjoyed early popularity in the constitutional treatment of cancer but have since been shown to be without value or it has been discovered that the original results failed to establish any true value. Szecsi (1912) found that a selenium-vanadium compound was the most active of the group of substances he employed in the treatment of mice with transplantable tumors. Keysser (1914), however, showed that while superficial tumors were cured, the substance was entirely inactive in treatment of infiltrating tumors of the organs and that it had no effect upon the tumor cells in vitro. Neuberg, Caspari, and Lohe (1912) claimed success in the treatment of animal tumors with cobalt and with platinum, the latter having also been investigated by Fleisher and Loeb (1914). Kolmer (1926) included tin among those metals which had had early

popularity but which had no substantial claim to effectiveness. Krause (1929) investigated the effect of a group of complex organic compounds of tin on mice with experimental carcinoma to determine the toxicity and chemotherapeutic effect. Regression of the tumor was noted in a small persentage of cases with two of the four compounds used.

LeGuyon (1931) found potassium chromate, sodium chromate, chromium phosphate, and basic aluminum acetate ineffective in treatment of the Jensen rat sarcoma. Ernst (1932) used a preparation containing lithium, magnesium and iodine, called RIII, in the treatment of fifty-four cases; no cures were claimed. Engman (1932), thinking that thallium acetate might affect young, actively growing cells, treated thirteen groups of five to fifteen rats each with the Flexner-Jobling carcinoma in a well controlled experiment. No effect occurred. Lansbury (1932) used the same tumor and found no effect from thallium phosphate, acetate and iodide. Gardner (1928) had good results with titanium employing a compound derived from the action of titanium chloride on a lipase solution combined with sodium oleate.

Shear (1933) made an extensive review of the role of potassium, sodium, calcium, and magnesium in cancer. He concluded that: sodium had no effect upon cancer, potassium may have a slight stimulating effect,

calcium possibly slightly retards the growth of cancer; the effect of magnesium has already been noted. In a later report, Shear (1934) noted that he was unable to affect the tumor cells with calcium.

IV

ADDITIONAL INORGANIC COMPOUNDS

SELENIUM.--Animal Tumors.--Selenium was the first substance to be used in the chemotherapt of cancer. Wassermann noted the staining of cells by eosin and combined it with selenium in the hope that the toxic selenium would be carried to the malignant cells by the eosin. Experiments with the substance upon transplantable and spontaneous rat tumors gave results which Wassermann considered sufficiently successful to report at a meeting of the Berlin Medical Society (Wassermann, Keysser, and Wassermann, 1911). Following this report, there was wide comment upon the possibilities of the substance (Editorials, 1912). Wassermann, however, had made no great claims concerning the efficacy of his preparation, and his report failed to state the toxicity and the percentage of animals treated successfully.

Soon a number of observers attempted to confirm this work. Uhlenhuth (1912), however, found that a group of compounds of selenium and various dyes had no effect on mouse and rat tumors, and Walker (1912) was unable to prepare an effective compound. Finally Keysser (1914), one of the partners in the original work reported by

Wassermann, found that the substance cured only a very low percentage of animals, that it was very highly toxic, that it had no effect on such small tumors as were not apt to undergo spontaneous central necrosis, that it had no effect on infiltrating tumors of organs or on metastases, and, finally, that it was totally ineffective in destroying tumor cells in vitro.

Human.--Following the early work on animals, several commercial selenium products were tested in cases of inoperable human cancer,--electro-selenium, seleniol, sulpho-selene, etc. Results were reported by a number of observers, symptomatic improvement being noted in the preliminary report of each in most cases. Follow-up reports stating the final results in these cases, however, have never been published. Watson-Williams (1919) summarized a group of these preliminary reports and was so favorably impressed that he employed a preparation called erythro-selenium beta in twenty-four cases. He observed these a short time and listed improvements noted in nineteen cases, but he has not reported on their final outcome.

After giving up the use of D4S, a compound of lead and selenium, Todd (1934) investigated a number of selenium compounds not containing lead. He used two substances in each case of inoperable cancer treated since May, 1931. One was prepared from selenium dioxide

and colloidal sulfur, called SSe, and always followed its administration with irradiation, claiming that the radient energy caused "ionization" of the SSe and thereby enhanced its value. The other substance, which was alternated with SSe, was selenium and some feebly radioactive substances, radium G and traces of higher breakdown products, prepared to form a colloidal solution called R. A. S. This latter preparation produced regressions in twenty-five percent of tumors in animals bearing a slow-growing strain of the Twort carcinoma. The first series consisted of ninety-three cases treated from May, 1931 to September, 1932. Eighteen discontinued treatment, five were recent cases, three were cured but died of intercurrent disease, and fifteen are living and well and have been discharged as cured. The second series included all cases treated from September, 1932 to date, numbering sixty-two in all. Twelve were recent cases, seven discontinued treatment, three were discharged as cured, and nine were under treatment and doing very well, some awaiting discharge. There are, then, about twenty percent cures in each series.

ARSENIC.--There are very few references to the use of arsenicals in the treatment of cancer. In view of its extensive use in the treatment of syphilis, this is difficult to explain. It seems probable that there were numerous early attempts to use arsenic in cancer but,

these being failures, were not reported.

Animal Tumors.--Uhlenhuth (1912) used annumber of arsenic preparations in the treatment of cancer in animals and found that stimulation of growth occurred. Eggers (1934) investigated the effect of compounds of arsenic and acids derived from a group of hexose sugars on the FRC carcinoma and the R39 rat sarcoma of the Crocker Institute. There had been previous attempts by several observers to employ metabolic peculiarities of the cancer cells as a basis for chemotherapeutic attack. Eggers used the abnormal carbohydrate metabolism discovered by Warburg (1931), by which an abnormal affinity or an altered mode of utilization of carbohydrates occurs in cancer cells. He employed sugars as carriers of toxic radicals in an effort to effect the elective intoxication of the cancer cells. While a compound containing a toxic redical attached to the side chain of the dextrose molecule would be theoretically best, there is no method at present of preparing such substance, so he was restricted to compounds of acids derived from sugars and tetramethyl arsonium as the toxic radical. Tetramethyl arsonium gluconate was the only successful compound. In eleven rats with the FRC carcinoma, five tumors completely disappeared, while four of ten with the R39 tumor disappeared. Next insulin was administered with the arsenical to temporarily diminish the available

supply of glucose in the blood. Tumors in nine of twelve animals with small FRC tumors completely disappeared, while five of six slightly larger tumors disappeared. Tumors in twenty-one of twenty-two animals with small R39 tumors disappeared, while four of twelve larger ones disappeared. None disappeared when very large tumors were treated. The only regularity was with three day implants. The toxicity of the compound is very low.

Human.--Dreuschuch and Lovas (1926) reported two cases of ovarian carcinoma treated by X-ray, a group of hormones and an arsenic preparation, with both patients alive and well two years. Eggers has treated several cases of human inoperable cancer with tetramethyl arsonium gluconate, but he considers the work too recent for evaluation of results.

SULFUR.--Animal Tumors.--Izar (1913) proposed colloidal sulfur for the treatment of implanted rat sarcoma. He found that rapid regression followed its intravenous use. Small tumors receded entirely, while large tumors became necrotic and death of the animal frequently followed, supposedly due to absorption of the toxic material liberated from the tumor cells. Zagni (1927) used a colloidal sulfur preparation called sulfosolo on a group of mice with experimental carcinoma and sarcoma. Two of the sarcomas disappeared, and some success was claimed with the carcinoma, but in no case was the total number of animals used given.

Human.--Cignozzi (1927) treated nearly one hundred cases with oral and intravenous administration of colloidal sulfur and noted some decrease in size of a few tumors. Surgical treatment and pre- or post-operative irradiation were combined in some cases.

MISCELLANEOUS.--Tellurium, because of its similarity to selenium, has been used experimentally in the treatment of cancer. Wassermann, Keysser, and Wassermann (1911) seemed much less impressed of its value than that of selenium. Uhlenhuth (1912) found tellurium and iodine compounds to be of no value in treatment of rat and mouse tumors. Rossi (1928) believed sodium silicate necessary for cicatrization and sclerotization, and that when employed with other methods of treatment might be valuable in aiding the natural defense of the organism. The results of his use of this substance are inconclusive. Woglom and Weber (1934) employed heavy water in doses equal to 120 times the usual daily intake of heavy hydrogen, given subcutaneously, intraperitoneally, and intravenously in mice with ~~carcinoma~~ sarcoma 180 and carcinoma 63. There was no effect on the host or tumor. Ishiwara, Marsh, and Simpson and Marsh, in papers previously referred to, included the use of a number of the inorganic substances reviewed above in their work.

V

ADDITIONAL ORGANIC COMPOUNDS

Benedict and Lewis (1914) reported some success in treating experimental tumors with toxic doses of phloridzin. Wood and McLean (1916) were unable to duplicate their findings on mice with spontaneous mammary carcinoma, the Crocker Fund mouse sarcoma 180, and the Buffalo rat carcinoma using non-toxic doses of phloridzin. Results with the first two tumors were about the same in the treated animals as in the controls, while with the Buffalo rat sarcoma, fewer tumors in treated animals were absorbed than the untreated controls. Werner (1912) found rat tumors reduced in size after injection of choline borate subcutaneously . He later switched to a mixture containing choline borate, which was found to be entirely without value. Fleisher and Loeb (1914) experimented with casein, nucleoproteid, and hirudin, which they thought caused some inhibition of growth of the tumors employed.

Karczag et al (1927) treated mice innoculated with the Ehrlich carcinoma with convulsive doses of potassium cyanide. They thought that this respiratory poison might have some selective effect on malignant

cells, based on the metabolic peculiarities discovered by Warburg. In ninety-eight mice treated, fourteen were cured, while none of forty-five untreated controls lived. Maxwell and Bischoff (1933) tested hydrocyanic acid on several tumors of rats and mice. In several series of mice with sarcoma 180, the rate of growth in the seventy-one controls was slightly greater than in the sixty treated animals. The rate of growth of tumors in rats with carcinoma 256 and sarcoma R10 appeared to be slightly decreased. There were no significant differences in the number of takes and the number of regressions found in mice bearing sarcoma 180 between those treated with carbon monoxide and the untreated controls. Perry (1935) found that prolonged inhalation of cyanide arrests body growth in young rats and retards the growth of the Jensen rat sarcoma. While a considerable percentage showed complete regression, the compound was very toxic.

A few of the amino acids have been tried. Vlès and his co-workers (1930) gave a mixture of alanine, cystine and proline to 107 mice with tar cancers following biopsy. Twenty-six disappeared, thirty-seven partially regressed, thirty-five remained stationary, and nine were unaffected. There were no regressions in forty-two controls. A series of twenty mice were treated with a mixture containing two molecules of d-glutamic acid to one of cystine. Ten disappeared and six partially regressed.

In a later paper (1934), they reported on the use of amino acids (l-cystine, d-l-alanine, and d-l-proline) combined with dried powdered tissues. More mammary carcinomas regressed than when amino acids were used alone. Fifteen of the thirty-eight tumors disappeared. In another report, however, they stated that the cured animals died sooner than others, due to breakdown of tumor tissue. Gilroy (1930) found that a transplantable mouse tumor was unaffected by glycine, alanine, cystine, cysteine, glutamic acid, sodium valerate and histidine. Argenine stimulated growth.

Marsh (1933) treated spontaneous mouse carcinomas with ethyl alcohol by intravenous, subcutaneous, and oral administration and by these methods in combination. None of the forty-nine treated animals showed any curative effect. Nakahara (1924) found that while sodium oleate, oleic acid, linolic acid and linolenic acid increased the resistance of mice to subsequent innoculation with the Bashford adenocarcinoma 63, there was no marked influence on established grafts.

Krontowski et al (1932) attempted to inhibit glycolysis of tumor cells with monoiodoacetic acid and monobromacetic acid. These compounds were effective <u>in vitro</u> but failed to retard the growth of the Ehrlich mouse carcinoma or the Jensen rat sarcoma in intact animals in doses consistent with the effective concen-

tration in vitro. Seele and Bodansky (1935) thought that similar substances having a greater permiability might be more effective. They treated rats bearing sarcoma 39 with relatively large doses of bromcaproic acid. Daily doses given for four weeks proved fatal to thirty to forty percent of the animals and had no specific inhibitory effect on the tumor.

Amoroso (1935) treated mice bearing carcinoma 63 with small quantities of colchicine. Two-thirds of the tumors of some series disappeared and all of those in other series regressed. An epithelioma of the buccal mucous membrane in a dog disappeared on treatment.

DYES

ISAMINE BLUE.--Animal Tumors.--This dye has been used by a number of experimenters in the treatment of inoperable human cancer since it was introduced by Roosen in 1923. Marsh and Simpson included it in a report on 145 coal tar dyes and their antecedents used in the treatment of albino house mice with spontaneous carcinoma of the breast. Practically every dye ever used to treat cancer is included in the list, and none subsequently mentioned in this paper were omitted. The results were uniformly entirely negative. Zadik (1930) claimed success in the treatment of transplantable rat carcinoma with pure isamine blue and bismuth.

Human.--Roosen (1923) observed some concentration of isamine blue in tumors. He argued that since the dye is very easily reduced in the body, injection of some very easily exidizable substance following administration of the dye might lead to formation of deleterious substances in the tumor cell. The easily oxidizable substance selected was neosalvarsan. The two were administered alternately at intervals of several days. The author claims good results, especially on small skin cancers. Sarcoma were found more susceptible than carcinoma. Internal tumors responded poorly. Irradiation destroyed the power of the tumor of absorbing the dye. Bernhardt, and Bernhardt and Strauch (1928) reported on eighteen cases treated with isamine blue. Five regressed, ten improved, and eight were not improved. Roosen, in 1930, advocated isamine blue alone rather than combined with bismuth ot irradiation, and has published a book summarizing the work done by a group of observers. Karrenberg (1929) had no regressions in five cases, and Zadik's results on human cases were only temporary. Nyka (1931) included isamine blue in a review of nine dyes used in the treatment of cancer and concluded that it was of doubtful value.

MISCELLANEOUS DYES.--Copeman (1928) reported on five cases of inoperable carcinoma of the breast, one of which completely disappeared under treatment by "activated"

flourescein. His idea was that administration of the dye followed by irradiation of the tumor produced an especially great effect effect on the tumor because of the effect of the irradiation on the dye. A later report on seventy cases was made by Copeman, Coke and Gouldesbrough (1929) and a final one by Copeman (1931) on 120 cases. Twenty-three of these apparently recovered. Mottram (1929) tested the effect of flourescein and irradiation on tumor tissue in vitro. He found that the action was purely a summation of the effects of the flourescein and irradiation.

Rossi (1928) included methylene blue with sodium silicate and magnesium sulfate in the treatment of inoperable tumors. The results are inconclusive and the value of the individual substances impossible to determine. Sugiura and Benedict (1929) studied the toxic action in vitro of malachite green, methylene blue, gentian violet and congo red on the Flexner-Jobling rat carcinoma, the Sugiura rat sarcoma and the Rous chicken sarcoma. While of some value, in the order listed, the authors did not seem particularly impressed.

VI

BIOLOGICAL PREPARATIONS

A. HORMONES AND TISSUE EXTRACTS

EXTRACTS OF THE SUPRARENAL GLANDS.--Anatomic and functional differences between the cortex and medulla of the suprarenal gland are now well established. While most preparations used in the treatment of cancer have been cortical extracts, some have used medullary extract and others mixtures. Coffey and Humber, whose much publicized work opened the controversy on the value of suprarenal cortex extract in the treatment of cancer, have published several reports (1930, 1931) on their work. It was based on the theory that the normal secretion of these structures controls tissue growth and can destroy malignant tissue. As far as it has been possible to determine, however, Coffey and Humber have at no time reported the number of cases treated, giving the information necessary for determining the percentage of cures, not have they given the basis they fave used for considering a case cured. Inasmuch as the reports by the originators of this method of treatment is concerned, then, there is no evidence of its value.

Animal Tumors.--Bischoff and Maxwell (1930, 1931)

employed eight preparations of suprarenal extract, including that of Coffey and Humber, on rats with sarcoma 10 and the Hyde carcinoma and found all to be without effect on the indidence of regressions and the rate of growth of the tumors. Woglom (1931) treated mice bearing carcinoma 63 and sarcoma 180 with suprarenal extract taken from rabbits treated with mouse tumor extracts and with a preparation from normal rabbits. There was no inhibitory effect. Sugiura (1931) used an aqueous extract of sheep suprarenal cortex prepared by the methed of Coffey and Humber in the treatment of animals with the Flexner-Jobling rat carcinoma, the Sugiura rat carcinoma, the Bashford mouse carcinoma 63, a transplantable mouse melanoma, and Rous chicken sarcoma, and spontaneous mammary carcinoma of the mouse. Subsutaneous and intramuscular, single and repeated injections had no curative, retarding or accelerating effect on the growth of the tumor or on the duration of life of the animal. Itami and McDonald (1930) could observe no effect on a spontaneous mouse tumor from the preparation they used.

Reicher (1910) claimed adrenalin injected intra-tumorally destroyed mouse carcinoma and rat sarcoma, while Uhlenhuth (1910) had found no therapeutic effect. Lumsden (1931) used it with a serum injection to prevent absorption of the serum. Tamura (1934) treated rats bearing the Flexner-Jobling carcinoma and rabbits bearing

the Kato sarcoma with a variety of extracts of the suprarenal gland. Large doses of the cortical preparation were slightly inhibitory, while adrenalin produced distinct transitory acceleration of growth. Sugiura and Benedict (1930) investigated the effect of suprarenal extract upon the Flexner-Jobling rat carcinoma and the Rous chicken sarcoma. They studied the effect of intratumoral injection, distal subsutaneous injection and application to the tumor cells in vitro. They found that intratumoral injection injibits small tumors completely but has no effect on larger ones; that remote subsutaneous injection has no effect, and that the Flexner-Jobling tumor is partially destroyed and the Rous sarcoma unaffected by application in vitro. They concluded that any possible value was limited to intratumoral injection.

Human.--Naame (1929) treated a group of patients with thyroid, liver and suprarenal extracts. He referred to six cases, two of which were claimed cured. M. Roussy, in discussion, stated that no effect had been produced in any case he treated. Livsic (1932) held that suprarenal cortex is employed in the defense against cancer by way of regulating lipoid metabolism, and he employed extracts thereof in the treatment of human cases. He gives reports on two cases that were apparently benefitted. Dominguez (1931) treated thirteen patients with adrenalin and suprarenal products especially prepared and noted no improvement

in any case. Harris (1931) undertook a clinical study of 415 cases with malignant tumors who had received experimental injection of the Coffey-Humber extract. There were 264 known dead in fourteen months; of the remainder, there was no evidence of any cures. Ball (1931) performed autopsies on 116 cases of malignant disease, eighty-nine of which had received experimental injections of the Coffey-Humber extract. No essential change from that usually observed in the characteristics of malignant disease in far advanced cases could be found in the tissues of the eighty-nine cases treated.

PITUITARY AND OVARIAN HORMONES.--Animal Tumors.--A group of Japanese investigators (Murohara, Motsuoka, Maeda, and Himento, 1930) found that the rate of growth of a transplantable rabbit sarcoma was retarded and the incidence of metastases reduced by the administration of follicular fluid. They reported the same results from large doses of thyroxin in potassium iodide and from thymoglandol. Bischoff and Maxwell (1930), however, treated rats with sarcoma 10 with the Alan-Doisy follicular preparation, corpus luteum extract, and three splenic extracts without effect on the incidence of regressions or the rate of growth in well controlled experiments. Later (1931), they reported on the use of placental and pregnant urine extracts, thyroxin, synthalin and parathormone on rats with sarcoma 10. All these

substances were ineffective. Gruhzit (1933) treated rats which had been innoculated with the Flexner-Jobling carcinoma with anterior pituitary hormone extracted from the urine of pregnant women. There was no significant difference in the course of the disease in the 124 treated animals and the 110 controls. Gross (1932) used extracts of urine of pregnant women and urine of women having cancer, hormones of the anterior pituitary, human and bovine placenta, and umbilical cord extracts on 321 mice having the Vienna sarcoma. There were no consistent specific results. In 1933, Maxwell and Bischoff treated fourteen mice bearing the sarcoma 180 with pituitrin, and noted no difference in the rate of growth in the treated animals and in the fifteen controls. Krehbiel, Haagensen, and Plantenga (1934) treated sixty animals who had been inoculated with mouse sarcoma 180 with an anterior pituitary hormone. Forty-five died during the period of observation of the experiment, and there was no evidence of improvement in the fifteen survivors. Tanzer (1936) reviewed much of the work done on the use of hormones in the treatment of cancer and called attention to hazards arising from the difficulties of differentiating direct and indirect effects. The indirect effects consist of malnutrition and sickness of animals. To eliminate such hazards, he set up experiments in which the tumor tissue was exposed directly to prolan extract

in vitro, following which inoculation was made into the host and a control inoculated into the same animal. He used follutein, a powdered prolan prepared by the method of Aschheim and Zondek and mouse sarcoma 180 and S37. With the former, there was no evidence of inhibition or acceleration of growth, while with the latter, there was slight inhibition of growth.

Human.--Susman (1931) postulated some increased secretion of the anterior pituitary in cases of malignant disease and sought to reduce this with pituitrin and theelin. Since abundant carbohydrate in the diet of mice promoted the development of irritation carcinoma, the carbohydrate intake was restricted. Reports on seven treated cases claim some improvement during the short period of observation. Ishihara (1934) was convinced that Wharton's jelly was an important structure, having an endocrine function, and that a similar hormone is to be found in the jelly between the inner and outer egg integuments of the placenta and in the corpus luteum of the ovary. He reported on the use of this substance, which he called "P. O. U." (placenta-ovary-umbilicus) hormone, in more than 200 cases, many of which appeared cured. Several have not relapsed in three years. A number of case reports are given. Stewart (1932) gave case reports on four patients treated with pituitary extracts without any beneficial effect, and Riches and

Kremer (1932) treated nine cases by the method of Susman, all their cases following the usual course of the disease with no regressions or prolongation of life.

MISCELLANEOUS.--Cioffari and Piccaluga (1926) treated mice before, after, and before and after inoculation with a tumor with insulin. Those treated both before and after inoculation showed some retardation of growth of the tumor, living ten to fifteen days longer than the other animals. No regressions occurred. Boivin (1927) treated one rabbit with tar cancer with insulin without beneficial effect. Fichera (1933) beleived cancer due to a disturbance of the tissues and organs which regulate cytolysis and sought to cure it by administration of a preparation containing extracts of the organs he found to increase cytolysis. He called this method "lytic regulating organotherapy". Over 300 cases have been treated of which over 100 were inoperable and ray-resistant cases with recurrences and metastases. Using only the biologic oncolytic regulating therapy, complete regressions occurred in nine percent of the cases and permanent stand-still of the tumor growth was observed in eight percent. Schulte and Lutteken (1935) treated sixty-one patients by Fichera's method and found none in any way improved. They comment that this is the usual finding of all except Fichera. Konsuloff (1934) treated mice bearing the Ehrlich tumor with a mixture prepared from

a splenic extract and alkaline earth metals. Of the 120 mice treated, slowing of growth occurred in fifty to eighty percent. As the computed volumes varied greatly in the treated animals and in the controls, they wisely refrained from reaching any definite conclusions from their results. Simpson and Marsh (1931) found karkinolysin, a thymic extract, to be without value in the treatment of a spontaneous mammary carcinoma of the mouse. Rohdenburg and Bullock (1915) noted that insufficient or excessive secretion of the thyroid, thymus, ovary, adrenal and pancreas had been thought causes of cancer, and extracts of these glands used in treatment. They reasoned that if functional changes are accompanied by histologic changes, controlled observation of the histoloty of these glands in animals bearing spontaneous tumors might throw some light on their role in the cause and cure of cancer. As a result of this line of thought, they examined the liver, kidney, spleen, pancreas, ovary, thymus, pituitary, parathyroid, thyroid, and adrenal of mice with spontaneous tumors and of controls. Their was no significant difference in these organs in the affected animals and the controls. Maisin and Pourboix (1935) reviewed the history of work with growth-promoting and growth-inhibiting substances extracted from normal organs.

B. VENOMS

It has been established that the venoms of some snakes have an analgesic action when administered in proper doses to cancer patients. The value of this method of producing analgesia as compared with the more standard procedures is disputed. Many papers have been published on this matter with no reference to cure of cancer, but as it was introduced as a method of cure, there have been numerous reports seeking to establish its value therein. Only those dealing with the latter phase of the subject will be considered here. Attention should be called, however, to the fact that besides the negative reports, the many instances in which it has been used as an analgesic without cure resulting detracts from the possibility of its having any curative value.

Animal Tumors.--Essex and Priestly (1931) investigated the effect of rattle snake venom on the Flexner-Jobling rat carcinoma and found it to be of no curative value. Grasset and dse Legneris (1934) found no constant inhibitory effect in vivo or in vitro on the Rous chicken sarcoma. The transitory effect on melanomas in an Angora goat and a horse were not maintained, perhaps because an antivenom was produced.

Human.--Piton (1934) treated fifty cases with only partial relief of pain and occasional transitory

arrest of the growth. He points out that Professor Billard, in about 1913, claimed success in treatment of one case of carcinoma with viper venom. Lavedan (1935) treated fifty-one cases of histologically confirmed cancer with cobra venom. Some cases received intramuscular injections, while others were treated by injection directly into the tumor. From his results as well as from those of others whose work he reviews he concludes that the relief from pain is irregular and inconstant, many patients experiencing no relief at all; that the action on tumors in man is nil; and that under these conditions, its use should be reserved for the rare cases in which morphine is ineffectual.

C. BACTERIA AND THEIR GROWTH PRODUCTS

It had long been noted that patients with cancer were often improved markedly following an attack of an acute febrile disease, especially erysipelas. Many of the cases in which spontaneous regression of established neoplasms had been reported had given a history of such attacks of febrile disease. Fehleisen (1883) discovered and proved the etiology of erysipelas and inoculated seven patients having advanced and hopeless cancers with Streptococcus erysipelas. Of the six in which the disease developed, the neoplasm became much improved in three. This is the earliest available record of the use of

specific constitutional methods of treatment of cancer in modern times. Lassar used sterile filtrates of Streptococcus erysipelas cultures in the attempt to treat human malignant disease in 1891. At the time, the method had not been placed upon an experimental basis, but soon afterwards Spronck (1892) treated animals bearing spontaneous neoplasms with killed cultures. While the results of these early works were not especially good, they led others, notably Coley, to investigate this field.

Animal Tumors.--Spronck (1892) treated animals bearing spontaneous tumors with killed cultures of Streptococcus erysipelas. He considered the results in a few cases encouraging. Beebe and Tracy (1907) made multiple inoculations of a transplantable lymphosarcoma into eleven dogs. Both the sterile culture and the filtrate of Staphylococcus pyogenes aureus, Streptococcus pyogenes, Bacillus prodigiosus, and Bacillus coli communis were used intratumorally and by injection distal to the tumors. Some of the tumors regressed partially and there were some complete recessions. Then, for a long period during which Coley's toxins were being used in a few human cases, interest in the experimental aspect of this subject lagged, until revived in 1931 by the work of Gratia and Linz.

They treated transplanted liposarcoma of the guinea pig with filtrates of Bacillus coli and obtained

hemorrhage and liquefaction in some tumors. Shwartzman had noted a skin reaction to meningococcus filtrate in a large percent of animals bearing neoplasms, which he considered of value as a serological method of diagnosis of cancer. In 1932, he (Shwartzman and Michailovsky) reported some complete regressions of mouse sarcoma 180 following administration of meningococcus filtrate. Later (1935), he studied the effect of spontaneous and induced infection on the development of mouse sarcoma 180. Bacillus enteriditis infection in 610 mice prevented the occurrence of growth of inoculated neoplasm in twenty-three percent of the animals at the end of the second week. Staphylococcus aureus was of no value, but Bacillus enteriditis (rough) caused complete regression of the tumor in eight of twenty animals. Staphylococcus aureus culture filtrate was also inactive, but the sterile filtrate of a culture of Bacillus enteriditis gave results similar to those of the live organism. Shear (1935), after studying a very large group of chemicals in the treatment of cancer, concluded that his best results were with bacterial filtrates. He tested agar washings of meningococcus filtrates with results which he considered encouraging, a few of the growths completely and permanently receeding. He stated that other experiments which were soon to be reported had given favorable results in upward to 100% of the treated animals. Duran-Reynals

(1933) undertook the study of the reaction of tumors to blood carried bacterial toxins. With Bacillus coli toxins he found rapidly growing transplantable malignant tumors of rats and mice to be susceptible, while slow growing were not. Later (1935), he treated fifty-two mice bearing proven mammary carcinoma with very toxic agar washings of human or mouse typhoid bacilli or both. Six were entirely inhibited, three cured and three recurred. Results were better in small tumors than in large ones.

Torrey and Kahn (1927) used the proteolytic enzymes of Bacillus sporogenes and Bacillus histolyticus to treat white rats inoculated with the Flexner-Jobling carcinoma. The former was dropped because of the unsatisfactory results obtained. Use of the live Bacillus histolyticus contained in whole broth cultures caused very energetic digestion which was not limited to the tumor. In their attempts to prepare a satisfactory sterile filtrate, they modified the medium, culture method, and concentration of the proteolytic ferment. Their best results were with a certain strain of the organism grown for twenty-four hours on a three to four percent peptone meat infusion broth by the Huntoon method with added fresh defibrinated blood, especially where a few living organisms were added. Fifty to seventy-five percent were cured where the skin was not too much in-

volved. As the injections were intratumoral, however, the method does not fall clearly into the field of constitutional treatment.

Spontaneous mammary carcinoma of the mouse were not benefitted by Tuberculin (Simpson and Marsh, 1931). Gye (1935) used ensol (see Connell, below) on appropriate mice and found it to be worthless. Roskin and Monanowa (1935) experimented with the use of several protozoan infections in the treatment of tumors of animals. They found that infection with Spironema duttoni or treatment with bacterial endotoxins ("pyrifer", from non-pathogens of the coli type) had no effect on an unspecified type of transplantable mouse carcinoma, and that Trypanosoma equiperdum was ineffective against an unidentified guinea pig tumor. Infection with Schizotrypanum cruzi and injection withethe sterile endotoxin retarded the growth of the mouse tumor. Forty-five mice were simultaneously inoculated with the tumor and infected with the organism; thirty growths disappeared and fifteen were retarded in growth but all the animals subsequently died of the infection. Forty animals were treated with the endotoxins alone; twenty-four grew and of these the rate of growth was considerably smaller in the treated group than in the controls.

Human.--Lassar (1891) was not impressed by the results he attained in the treatment of two cases of

human cancer with sterile filtrates of Streptococcus erysipelas. Coley (1891), however, noting the observations of others regarding the results of accidental ot deliberate production of erysipelas in cancer patients, treated several such patients by inoculation with the disease and considered his results sufficiently good to warrent further trial. By 1893, he had collected records of forty-seven cases of cancer patients (ten of which were personal cases) that had been accidentally or deliberately inoculated with Streptococcus erysipelas. He concluded that the curative effect in some cases was an established fact; that sarcoma patients were more often benefitted than carcinoma patients, in a ratio of about three to one; that the treatment was not dangerous; and that the effect was due to the systemic action of the toxins of the organism. A note appended to this article stated that the toxins of the organism combined with those of Bacillus prodigiosus were being tried and would be reported soon. This latter combination became known as Coley's toxins. Several reports were made in the following years by Coley as well as by a number of other physicians who had tried the Coley treatment. While some denied any value whatever in the method, the majority found that the treatment was of some benefit in a small percentage of cases. Coley reported on the late results in his early successful cases as well as on

the successful cases reported in the literature by 1906. Twenty-four of Coley's cases were living and well three to thirteen years, and twenty-seven cases of other physicians were living and well three to twelve years. At the time, only sarcoma were considered sufficiently benefitted to warrent treatment. Coley's toxins were admitted to New and Non-official Remedies in 1910. The council's report stated that four to nine percent of the cases treated were cured. The product was reconsidered and retained by the council in 1934 following consideration of numerous pro and con reports on its value. The council concluded that use of the mixed toxins may prevent or retard recurrences or metastases, that an occasional cure may result in an otherwise hopeless case, and that the value is probably limited to tumors of entodermal or mesodermal dirivation, especially bone tumors without marked osteoplasia. Coley's later reports (1927, 1928, 1931) dealt for the most part with bone tumors. His results show that irradiation or amputation alone cannot be expected to cure cases of bone sarcoma, but that toxins and amputation cure a large percent of cases including many in which new bone formation occurs, that the toxins and irradiation cure some cases in which new bone formation does not occur, and that toxins alone have cured a few cases. The case of Christian and Palmer (1927, 1928) is an example of a recurrent myelosarcoma

(endothelial myeloma?) successfully treated by toxins alone. Campbell (1935) analysed a group of 125 patients with primary malignant bone tumors, fourteen of which were living and well five years or more. Ten were osteogenic sarcoma and four were non-osteogenic. Coley's toxins were used in four cases,--one case of vary malignant osteogenic sarcoma was living and well four and one half years following amputation and toxins; three cases of endothelial myeloma (Ewing's tumor) were living and well four, five and eight years following treatment with Coley's toxins combined in each case with amputation, irradiation, or both.

Coley (1928) reported the end results in the treatment of thirty-nine cases of Hodgkin's disease and fifty-eight cases of lymphosarcoma, where the mixed toxins alone or the toxins combined with irradiation were used. Three of the former and six of the latter were in good health three or more years.

Connell (1935) treated a group of animals and patients with a solution prepared as a filtrate of the growth products of Bacillus histolyticus grown on cancer tissue of the same type as the growth to be treated. Although the statistics were not given and the period of observation was short, the author concluded that the substance was valuable. He called it "ensol" (enzyme solution). Pearl, Sutton and Howard (1929) treated

seven cases with subcutaneous injections of tuberculin. They thought the size of the tumors to be reduced and the life of the patients prolonged, but claimed no cures.

D. MISCELLANEOUS

Whitehouse (1927) reported a case of ovarian carcinoma with peritoneal metastases treated by transfusion of blood of a woman ten weeks pregnant and transfusion of irradiated ascitic fluid. Intensive regression followed. Dziembowski (1930) treated 120 patients by injecting irradiated autogenous blood into the tumor and intravenously. At the time the results were not discussed, but in a later report (1931), cures were claimed in a few cases. Hyde (1935) reported on the use of irradiated autogenous blood in advanced cases of cancer following incomplete extirpation of the growth. The injection is made intravenously after irradiation of the blood. The number of cases treated was not given nor were the number of cures, but the author refers to several cases greatly benefitted.

VII

MISCELLANEOUS METHODS

FEVER THERAPY.--The classification of certain methods of treatment of cancer presents some difficulties because similar methods differ in the theories of their action. Thus, methods will be included here that may seem to belong elsewhere, but the substances herein reviewed are arbitrarily classified, for the most part, according to the theory of action advanced by the various individual investigators. In no case, however, is a single substance or method considered under two topics because of differences in the theories of action advanced.

Animal Tumors.--Rohdenburg and Prime (1921) studied the effects of combined heat and radiation on transplantable tumors in vitro and on spontaneous tumors in vivo. They found that low degrees of heat continued sufficiently long were 100% effective in killing cancer cells in vitro and that heat combined with irradiation extended the usefulness of the latter. They note that reports on fever treatment of malignant tumors had been made years previous by Loeb, 1912; Jensen, 1903; and Clowes, 1906. Woglom followed this with a study of body temperature and tumor growth in 1924, but because the results were negative, they were not reported until 1934,

by which time some favorable reports had accumulated. Woglom investigated the effect of febrile temperatures on seventy-seven rats with the Flexner-Jobling carcinoma or the Jensen sarcoma and on thirty-nine mice with carcinoma 63 or sarcoma 180. Eighteen experiments were performed in which different temperatures and different exposure times, varying from thirty-one to a total of 348 hours, were employed. No adverse effect upon the tumor was noted in any case. Walker (1935), who had previously found that exposure of rat tumor 256 to a temperature of 111.4° in vitro uniformly prevented takes on subsequent implantation, kept twenty-six animals at that temperature for twenty minutes. The tumors from each of the six rats that survived the twenty minutes (but which died within eight hours) were implanted into eight rats at the time of the death of the animal While controls grew in each instance, only two of the forty-eight treated tumors grew. Thirty minutes at 109° four times had no effect on the tumor. When the temperature was maintained at 111.4° by means of a high frequency apparatus, none of the thirty-five animals survived twenty minutes. Practically all of the tumors had been devitalized at the time of the death of the animal as noted by failure to take on implantation.

Human.--Braunstein (1931) inoculated six patients with the tertian malarial parasite and noted distinct but

transient regression of the tumor. Warren (1935) undertook a rather extensive study of the effect of artificial fever on hopeless tumor cases. He studied the effects of febrile temperature on animal tumors in vitro and in vivo; the temperature gradient during local and general heating; and the effects of prolonged and maintained generalized artificial fever in hopeless tumor cases with metastases. His in vitro experiments showed that there is a definite lethal time-temperature for malignant tissue as there is for the gonococcus and the Treponema pallidum. Animals did not endure the necessary temperature for the time indicated by the in vitro experiments to be the thermal death time. In his human cases, he first used diathermy and later radient energy, raising the temperature to 41.5°. Of the thirty-two cases treated, thirty were proven malignancy. The observation period extended twenty-three months, and all but three relatively recent cases had died, with one exception, within thirteen months. Doux (1935) reported a case of proven osteogenic sarcoma of the clavicle hiving deep X-ray and eight fever treatments at weekly intervals, at which times the rectal temperature was maintained at 105-106° for five hours. Steady and continuous improvement ensued and the patient was working and apparently well at the end of an observation period of slightly more than a year. In discussion, Dr. Bierman stated that a case of cancer of the lung was

alive three years following fever therapy.

A book published by Wiley Meyer in 1931 is interesting from the standpoint of fever therapy in cancer, but as no new experimental work is presented, it is not discussed here.

GASES.--Campbell (1931) makes a critical review of the use of gas mixtures in cancer therapy. Inhalation of gas containing a high percentage of oxygen as recommended by Campbell and Cramer; increased atmospheric pressure studied by Fischer and 5% carbon dioxide in oxygen reported by Fischer-Wasels as well as a number of others were reviewed. He concludes that there is no evidence of any influence on tumors or their metastases. DeAlmeida (1934) treated rats bearing the Roffo sarcoma. Seven to twenty-three percent of the animals were cured by oxygen at one to eight atmospheres treated at twenty minute to twenty-four hour intervals. Some tumors were completely destroyed, but there was a heavy mortality in the treated animals.

WATER BALANCE.--Shear has undertaken a number of fundamental studies of the chemistry of tumors with view to discovering a method of chemical treatment. Reference has already been made to his studies of the role of sodium, potassium, calcium, and magnesium in cancer and to the findings as to the effect of bacterial filtrates. The latter study (1935) was part of an investigation of

disturbances of fluid exchange on transplantable mouse tumors. He had studied such matters in in vitro experiments (Shear and Fogg, 1934) and the present paper reports results of tests of the methods in vivo on mice bearing sarcoma 180 or carcinoma 63. His results with deprivation of water, use of diuretics and massive bleeding were negative, so he attempted to alter the permiability of the cancer cells. To do this, the following substances were administered with the results noted: histamine, tyramine, trimethylamine, indole, skatol and choline with negative results; pneumococcus anitbody and soluble specific carbohydrate, with some effect--hemorrhage; bacterial filtrates, as have been noted, with striking results; lipoid solvents including alcohol, ether, chloroform, carbon tetrachloride, bile salts, and lecithin with negative results; sodium oleate with some effect; fibrin, sodium citrate and heparin with negative results; high protein diets and injection of agar, acacia, egg albumen, and serum albumen caused a few recessions; repeated horse serum injections into seventeen animals caused three complete recessions. The author admitted that many of the substances used here may have actions which are not entirely dependent on their effect on fluid exchange, but he considered this the most important action of each for reasons given.

VIII

DISCUSSION

It seems desirable to discuss the substances and methods reviewed in an attempt to estimate their value. But before entering into a discussion of the individual substances employed, certain facts must be pointed out.

Essential data are not given in many reports, making it impossible to evaluate substances in the light of any preconcieved criteria, such as those of Weil or of the health organization of the League of Nations. But of the manyssubstances considered, by far the largest share can be dismissed without detailed analysis because of glaring lack of adequate scientific evidence of effectiveness. In such cases, we must take the attitude that s substance is of no value unless proven so by scientific observations, that is, the burden of proof rests with those claiming effectiveness.

The significance of negative results is important. Where such results with identical compounds are overwhelming, especially where there have been few positive results reported or where the previous reports have arrived at positive conclusions without justification, we must conclude that the substance is without value.

However, as has been pointed out by Marsh and Simpson, negative results with a single compound of an element and under a narrow range of experimental conditions do not establish the lack of value of that element, for variation of the compounds used or of the details of the experiment might yield different results. Thus, conclusions must be limited to the circumstances of the experiment, except inasmuch as they yield suggestions for other possible useful experiments.

The purpose of all work on methods of constitutional treatment of cancer is to discover a substance that may be used successfully in human cases, thereby reaching beyond the present limits of surgery and irradiation. Successful results with animal experiments are, therefore, valuable as leads, pointing to those substances which may prove of value in human cases. This useful aid makes possible the investigation of a great many substances and should be employed in every case before human material is used.

Of the metallic preparations, lead and gold seem to merit consideration. While most of the animal experiments with lead compounds have been negative, the results of Collier and Krause with complex organic compounds of lead are moderately successful and further work with them is indicated. The principal claims are made for lead in the clinical field, much work having

been done with human subjects. All that can be said is that some observers have reported five to ten percent cures in otherwise hopeless cases, while others have been unable to note any useful results whatever. One can hardly reach any conclusions as to its value is view of such markedly conflicting reports, and further work is indicated, probably using some compound whose effectiveness can be established by animal experimentation. No favorable experimental work has been done on gold, but in view of Ochsner's reports of human cases, further work should be undertaken. The results with the remainder of the metals are entirely unsatisfactory, and as far as evidence at present is concerned, one may conclude that they are entirely without value.

Of the non-metallic inorganic compounds, those of selenium and arsenic merit consideration. The sole claim of the former rests with the unconfirmed observations of Todd, and its value is inconclusive until further work is done. Eggers results with tetramethyl arsonium gluconate show it to be clearly the most effective substance yet produced in the treatment of animal tumors. His results, of course, await confirmation and trial in human cases to establish the value of his compound.

Results with most of the organic compounds including a group of dyes have been most disappointing.

Some effect has been noted with amino acids and colchicine, but these await confirmation. While hormones have been rather generally discredited, the results of Ishihara with P. O. U. hormone should be checked.

Some striking effects have been produced by bacterial growth products in animals. Especially has this been noted with filtrates of the meningococcus and Bacillus enteriditis, employed by Shwartzman; the meningococcus filtrates used by Shear; and Bacillus coli and typhosus used by Duran-Reynals. Coley's toxins have stood the test of time and are the sole chemotherapeutic cancer treatment having official recognition. While thier field of usefulness is limited to sarcoma, especially those of the bones, a definite small percentage of cases are cured or greatly benefitted by their use. Their effectiveness cannot be denied, but they are effective in such a small percentage of the cases, that they cannot be considered specific.

Marked beneficial effect was noted by two investigators working separately with irradiated autogenous blood in human cases. Further work with this method is indicated.

At present, any possible value in fever therapy seems improbable. Some thorough, well controlled experiments show that the thermal death time of a group of tumors exceeds that of the hosts, and human work has

been quite unsuccessful. Gases have shown very little therapeutic action. The water balance experiments of Shear were negative except for those in which bacterial growth products were used, these having already been discussed.

Certain general criticisms of the work reviewed may be made. These are: reports on experiments in which too few subjects, human or animal, were used; failure to employ controls in numerous of the animal experiments; failure to give information necessary for independent evaluation of results; use of combined forms of treatment which renders evaluation of the individual substances impossible; and reaching conclusions which are broader than the results of the experimental work justify.

In again examining the reports reviewed, it can safely be concluded that, while some substances have undoubtedly produced cures in a small portion of the animal and human tumors treated, no method has so far been proven effective in the constitutional treatment of cancer. There are a number of substances which are quite promising and on which further evidence should be gathered.

IX

SUMMARY

(1). The need for and rational of specific constitutional methods of treatment of cancer is presented.

(2). The history of the subject is given.

(3). The substances and methods which have been used in animal and human cancer are classified and their results reviewed.

(4). General criticisms of the investigations reviewed are made.

(5). Some substances have been shown to have cured otherwise hopeless cases of cancer, and early results with a few substances suggest that they may eventually be proven of value.

(6). There is at present, however, no proven effective specific constitutional treatment of cancer.

THE SPECIFIC CONSTITUTIONAL TREATMENT OF CANCER

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