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EXPERIMENTAL CANCER, AN HISTORICAL RETROSPECT*

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INTRODUCTION

THE steady increase of cancer throughout the civilized world, coincident with the diminution or disappearance of many of the other field officers of the "Men of Death," have combined to focus attention on malignant disease as very nearly the most important single plague with which mankind now has to contend. Consideration, therefore, of one of the most important ways of studying this problem should not be untimely or unprofitable.

Fig. 1. Johannes Müller.

Cancer has been recognized since early antiquity; the Egyptians (Ebers Papyrus) and Hippocrates (see terms *Carcinos,* an inflammatory swelling and *Carcinoma,* a true neoplasm) were familiar with its external manifestations at least. Celsus not only recognized some of its visceral forms, but went far in differentiating it from benign neoplasms and inflammatory swellings. The ubiquitous Galen of course observed cancer with some accuracy, but hindered the progress of medical knowledge on the subject for centuries by the dominance of his doctrine of the four humors. To him cancer was due to the concentration of *atra bilis,* or black bile, and this, or similar nebulous hypotheses, sufficed as an explanation of its cause for many centuries. Following the discovery of the circulation of the blood and of lymph vessels, Malpighi, Louis, Le Dran and Astruc developed the idea that cancer was caused by coagulating and degenerating lymph; and even the astute Morgagni and John Hunter were unable to replace this view.

In this way the conception of cancer as a general disease, or as due to a special diathesis, persisted until the nineteenth century, when with the advent of the cell theory (*omnis cellula e cellula*) Johannes Müller and Virchow convinced the world that cancer consisted of an abnormal growth of abnormal cells. Again hypotheses as to the underlying cause of this abnormality became rife. This is not the place to do more than mention some of these; and at any rate the principal ones, Virchow's chronic irrita-

*Presidential Address: Philadelphia Pathological Society, Jan. 8, 1925.

tion theory, Cohnheim's stimulation of misplaced embryonal nests with Ribbert's later modification, heredity and the parasitic theory are too well known to you to require further notice at the moment. These natural outgrowths of the developing study of morbid anatomy and bacteriology have contributed greatly to the nosology, morphology, histogenesis and natural history of tumors, but for some years now have not seemed capable of taking us much further in our knowledge of the etiology of malignant tumors.

The experimental method, then, in this field, as in so many others, seems to offer the most promise in elucidating this mystery which is of such enormous importance to the human race. For although occasionally the means of successfully combating a disease is accidentally found before its cause is known, more often discovery of the cause must precede discovery of a fundamental method of treatment.

In the experimental field, perhaps the earliest and today the most profitable essays have been along the line of the experimental production of tumors in animals. Begun toward the middle of the last century, it was soon found that tumors of one species would not grow in animals of a different species and that transplantation of adult tissues even into animals of the same species was soon followed by absorption (Zahn, Leopold), whereas transplanted embryonal tissue might persist indefinitely and proliferate, though it lacked some of the characteristics of tumor growth (L. Loeb, Fichera). From Cohnheim's conception of embryonal rests, Askanazy educed the theorem: "Embryonal tissue separated by space as well as time may give rise to tumors," and submitted it to experimental proof by injecting intraperitoneally an emulsion of embryos of the same species. This produced in many different species the semineoplastic condition named "teratoid" (first obtained by Feré in 1897), and in three such animals Askanazy found that carcinoma later developed. He was properly cautious, however, in deciding whether this was due to a carcinomatous change in the teratoid itself, or in the tissues of the host due to the irritation of the teratoid.

Tumor material was first successfully transplanted into another animal of the same species by Hanau[2] in 1889. From a white rat several hours after its death from epithelioma of the vulva, with metastasis to both axillary and inguinal lymph-nodes, he transplanted bits of the tumor into the tunica vaginalis of two old rats. Both of these grew and another successful transplantation was made into the third generation. Hanau attributed the previous failures of other investigators to technical errors and to the injection subcutaneously rather than into lymph-spaces. Until the next

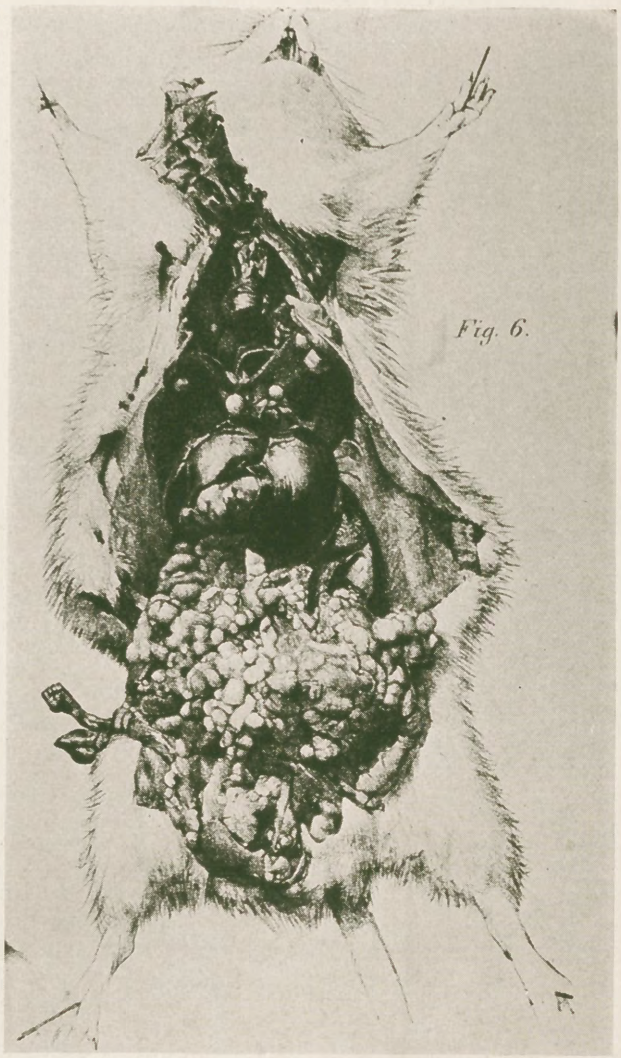

Fig. 2. A "Teratoid" Tumor in a Rat, Produced by Injecting Embryonic Emulsion.

century, however, the importance of this experiment, which opened a new and fertile line of research, was not recognized in spite of its confirmation and amplification by Morau,[3] von Eiselsberg,[4] Firket[5] and Velich[6] in the next decade. In 1901 Leo Loeb[7] in this country and Jensen[8] in 1903 in Denmark published work which established the inoculability of cancer as an accepted fact and

Fig. 3. Rudolf Virchow [1821–1902].

thus permitted the study of the cancer problem from a new biological point of view. Loeb, having found a cystic sarcoma of the thyroid of a white rat, successfully inoculated it into other rats and carried it through forty generations in twenty months, without change in its histological structure. In numerous communications he was a pioneer in furnishing evidence on many factors, such as the effect of temperature, infection, recession of growth, spontaneous disappearance, age, race, sex of animals and so forth, which influence the growth of transplanted tumors. Jensen's studies were even more important in emphasizing the importance of this method to European investigators. He not only succeeded in transmitting a typical mouse cancer through nineteen generations over a period of two and one-half years, with thirty to sixty per cent successful takes; but reported observations on the persistence of histological structure, frequency of mitoses, absence of metastases and of microorganisms, resistance of the cancer cell to various agents, the conditions of successful transplantation and similar topics. (The account of his rat sarcoma, which is probably the most used experimental tumor in Europe today, was published several years later.)[9]

The stimulus given to cancer study by this work was quickly reflected in the formation of new societies, institutes and journals. The *Zeitschrift für Krebsforschung* was started in 1903 by the Zentralkomitee zur Erforschung und Bekämpfung der Krebskrankheit (1900); the *Reports of the Imperial Cancer Research Fund* by Bashoford in 1904 (founded 1901); the *Bulletin de L'Association Française pour l'Étude du Cancer* in 1908; *Tumori* by Fichera in 1911; *Gann, Ergebnisse der Krebsforschung in Japan;* the *Studies in Cancer* of the Crocker Research Fund by F. C. Wood in 1912; and the *Journal of Cancer Research* in 1916, the last named being the official organ of the American Association for Cancer Research. The New York Memorial Hospital for the Treatment of Cancer (reorganized 1899), the New York State Institute for the Study of Malignant Disease (1899), the Institute of Cancer Research of Columbia University (1911), the St. Louis Cancer Hospital, the Huntington Memorial Hospital in Boston and the Radiological Department of the Philadelphia General Hospital (1921) in this country and the Middlesex Hospital Cancer Research Institute (1909), the Radium Institute (1911), and the Cancer Hospital in London are indicative of the intensive manner in which the cancer problem is now being studied.

Although the successful growth of inoculated tumors in animals was as necessary and important a step in cancer research as the methods of pure culture were for the early study of bacteriology, nevertheless this method was soon found to have obvious limitations. The transplanted tumor grew, to be sure, and eventually killed the host, but was found to behave so differently from spontaneous tumors in several ways, that it was always questionable whether observations and deductions elicited by this method could fairly be translated to the problems of spontaneous cancer. Such transplanted tumors rarely metastasized and although necessarily connected with the host by considerable vascular connections, they were definitely encapsulated and, as far as I know, nervous connections with the body of the host have never been demonstrated. Nevertheless a permanent and constant source of tumor supply had for the first time become available, by which the problems of virulence and adaptation, individual and family resistance, heredity, growth of tumor cells *in vitro*, the effects of diet, metabolism, tissue chemistry, meteorological influences and countless other variants could be submitted to scientific investigation.

The second big advance in the experimental study of cancer, also constituting a new era in cancer research, was Fibiger's[10] discovery that "spontaneous" gastric carcinoma could be produced at will by feeding to rats the larvae of a nematode worm. As an example of patient and ingenious research, his method deserves detailed notice. Having observed spontaneous gastric carcinomata in three rats that had been inoculated with tubercle bacilli, he endeavored unsuccessfully to propagate the tumor by inoculation into other rats. Minute study of the tumor sections having shown a peculiar structure that looked somewhat like the cross section of a parasite, he reconstructed a model from serial sections, to find that he was dealing with a nematode, which he later dissected in the gross and named spiroptera neoplastica. Further trouble awaited him in its identification, however. More than a thousand rats were sacrificed and carefully studied without finding tumor and parasite again. At length in the literature of animal parasites, he read that Galeb had secured nematodes in rats' stomachs by feeding them the common cockroach (Periplaneta orientalis), which was the host for this worm in another stage of its life cycle. His attempt to secure the worm's development in this way failed, however.

When the sustaining hope was almost gone, he heard of a large sugar refinery in the town, where both rats and cockroaches swarmed. The cockroaches here were of a different kind; they were P. americana, uncommon in Northern Europe. An examination of the rats revealed many cases of gastric tumors, and in them the long-sought-for nematode was found. A false clue and a stroke of fortune that was bravely deserved, led him to the great discovery. These cockroaches had come in consignments of sugar from the West Indies; in their muscles were the coiled-up larvae of the nematode and when the cockroaches were eaten by the rat the larvae were set free and developed in the stomach into the adult nematode. Here, after a time, it produced eggs which were evacuated with the faeces, eaten by the cockroach, and the larval stage again produced, and so the cycle went on (Leitch).[12]

Though the success of the experiment was said to have been further endangered by the burning-down of the sugar refinery, he was able to keep the supply going, and, by feeding cockroaches with ova and then feeding rats with the bodies of the infested cockroaches, he produced, first inflammatory changes, then papillomata and finally true carcinoma. The acuteness of observation, the "prepared mind," fertility in method of attack, patience in obtaining data, courage in the face of failure, judgment in drawing conclusions, all contributed to this really great investigation—to Leitch's mind, the greatest contribution to experimental medicine of this generation. Of the experimental rats that survived for more than two months, more than half developed carcinoma, after intervals of forty-five to sixty-six days. In one case metastasis occurred in one-hundred and four days. The resulting tumors were large, papillomatous overgrowths of epithelium with considerable keratosis, which filled the stomach cavity even to occlusion. The usually invasive properties of carcinoma were present and it is significant that no ova or parasites were found in the metastases.

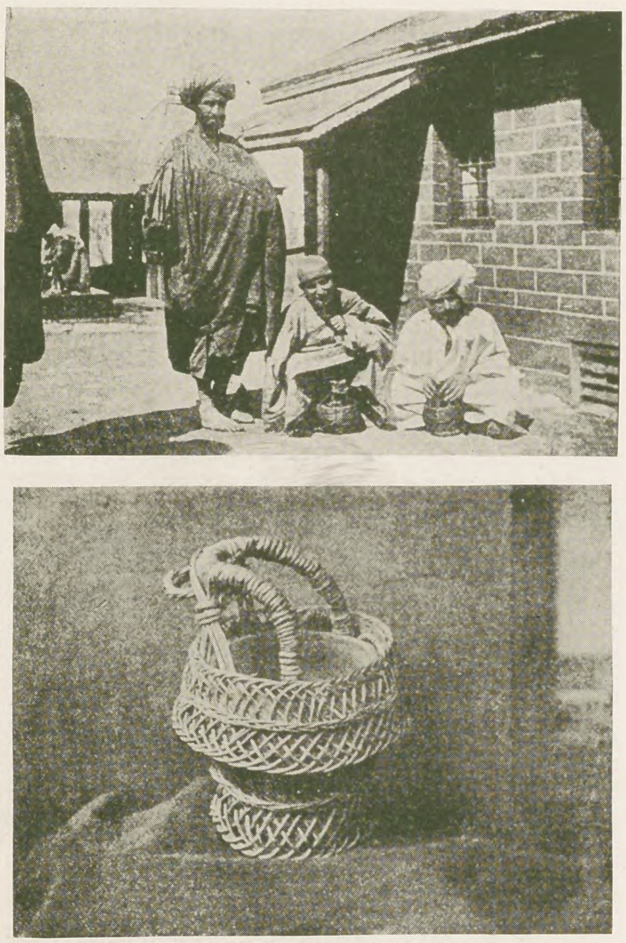

Fig. 4. Natives of Kashmir and Kangri Basket.

The ability thus to produce a real cancer almost at will constituted a great advance in that it overcame many of the limitations unavoidably associated with the inoculated tumors.

As experimental material, however, the stomach cancer was not especially suitable. The discovery, therefore, by Yamagiva and Ichikawa,[11] Japanese investigators who were stimulated by Fibiger's work and by the prevalence of cancer in tar workers, that a true skin cancer could be produced by repeated painting with coal tar, also constituted an important advance. By applying the tar every other day over periods of fifty-five to three-hundred and sixty days, either on the inner or outer surfaces of rabbits' ears, they succeeded in producing horny papillomatous growths, which in seven cases progressed to true cancer and in two metastasized. Later investigators have amply confirmed the possibility of producing cancer with tar, but have shown that the mouse constitutes a more favorable subject for this experiment. The frequency and amount of dosage, the best form of tar to be used and similar details are rapidly being worked out. An interesting development of the tar-cancer work is Murray's recent observation that whereas a tar tumor can never be induced in a mouse that already bears one, if the secondary applications are started at just the right time after the primary, tumors are induced with even greater ease, i.e., a temporary period of susceptibility exists.

In similar vein, Leitch has been able to produce true carcinoma of the skin by repeated administration of arsenic and of paraffin (shale oil), and has also produced carcinoma of the gall-bladder of a guinea pig by inserting human gallstones. Bulloch and Rohdenburg's[13] rat sarcoma of the liver following ingestion of Cysticercus fasciolaris (the larva of the cat tapeworm Taenia Crassicollis) is another achievement in the same line. Such experiments, together with the well-known clinical observations of the prevalence of cancer in chimney-sweeps, workers in tar, aniline dyes and paraffin, betel-nut chewers, the Kangri basket carriers of Kashmir, smoker's cancer of the lip, Bilharzia disease, *x*-ray and radium workers and similar irritating occupations, all point strongly to Virchow's old theory that cancer is due to a chronic irritation. We can be sure that that is not the whole story, as many of those exposed to these irritants fail to develop cancer and many irritants apparently have no carcinogenic influence, just as many bacteria are not in the least pathogenic. The probability, however, remains very strong that some form of irritation is at least an essential factor in so disturbing the normal development of cells that they undergo malignant change.

When tar cancer, for instance, can be produced in a big percentage of tests at any designated spot of the body, how can it be maintained that it was due to the sudden activity of Cohnheim embryonal rests, unless these are considered to be so ubiquitous as practically to lose significance. Even then the effect of the stimulus must also be taken into account.

More careful study of spontaneous animal tumors has shown that they are much more numerous than previously supposed. In fact two American investigators have conducted long series of studies on spontaneous tumors alone. Besides various mammals, birds, fish and even lower animals have been found to be subject to tumors of various kinds.

The ability to obtain experimental cancer material in animals at will by the methods previously described has resulted in many new phases of study of the cancer problem, which cannot be discussed here. The study of the host's resistance, however, and of the growth of tissue cells *in vitro* cannot be overlooked.

Just as it takes two parties to make a bargain or a fight or an infection, so it is claimed with some reason that it takes two parties to produce and maintain a tumor: the tumor itself and the host in which it is growing. Factors that stimulate, inhibit or prevent tumor growth are sufficiently numerous to make it logical to expect that further study of these mysteries will not only throw light on the nature of tumor growth but possibly afford a clinical means of slowing or preventing it entirely. Individual tumors are known to vary greatly in their speed of growth at different times; the young are much less susceptible to cancer than the old, and experimentally it was early found that something stopped tumors of one species from growing when transplanted into another species. By the use of the transplantation method, it was next found that animals once successfully inoculated were resistant to a second inoculation (Bashford)[14] and even that a resistant state could be induced by the injection of intact living cells of normal tissues. Disintegrated or dead cells were inactive and the resistance only seemed to apply to subsequent transplants, not to spontaneous tumors or transplants already established. Radiation of tumor cells has been tried as a means of stimulating immunity to tumor growth, and Contamin[15] and Wedd, Morson and Russ[16] believed that they had secured a certain degree of immunity in this way. More recently Chambers, Scott and Russ[17] found that with an accurately measured dose of radiation (a "rad," i.e., just enough to prevent the tumor cell from surviving) upon inoculation into animals, substances are given off which not only hinder or prevent the growth of subsequent inoculations, but in their hands have materially hindered the growth even of an established tumor. In fact, they have even had encouraging results in the clinical treatment of cancer by this method, although it must be admitted that in other hands it has failed to prove of value.

The extensive and ingenious work of Murphy[18] and his associates at the Rockefeller Institute has demonstrated the importance of the host from a very different point of view. Impressed with the close relation of the lymphocytes to tumor growth and resorption, they have devised numerous experiments to elucidate the significance of this relationship.

> The chick embryo, which normally lacks the ability to destroy a heteroplastic tissue graft, if supplied with a bit of adult lymphoid tissue becomes as resistant as the adult . . . An adult animal deprived of the major portion of its lymphoid system by repeated small doses of *x*-ray, no longer has the power to destroy a graft of foreign tissue and this tissue will grow actively. The chief characteristic of a failing heteroplastic graft in the unsuitable host is a marked accumulation of lymphocytes . . .

there is also a lymphocytic crisis in the circulating blood.

If a cancer is removed by operation, and the animal subjected to small "stimulating" doses of *x*-ray, the reinoculated cancer is said not to develop on account of the lymphocytosis produced, whereas in the controls, the cancer graft though submitted to the same dose of *x*-ray outside the body, when returned to the host grows as usual. "Autografts from spontaneous cancers of mice when replanted into areas previously exposed to an erythema dose of *x*-rays, failed to grow in the majority of instances, while similar grafts inoculated into untreated areas grew in a large proportion of the animals." A dosage of *x*-ray sufficient to kill an autograft *in situ*, failed to do so on similar tissue, if rayed outside of the body, or if after being rayed *in situ*, it was transplanted elsewhere, the inference of course being that death was brought about in the first instance by the effect on the bed and not on the cancer cells themselves. These and similar experiments, too numerous to mention here, if confirmed by other investigators (and it is only fair to say that in some details they have not been), show great promise in advancing our knowledge of the body's resistance to cancer.

The method of growing pure tissue cultures *in vitro*, attempted by Leo Loeb in 1898, made practical by Ross Harrison and improved by Burrowes, Carrel and others, is showing promising developments in cancer research. Not only has it been possible to grow pure cultures of carcinoma and sarcoma cells in this way, but some of their capabilities for pernicious growth have been demonstrated. Under ordinary conditions they grow so fast that they quickly degenerate and die out, but Fischer has recently succeeded in making them grow indefinitely by adding normal chicken muscle to the culture. It seems as if the tumor cells could utilize the normal cell protoplasm, whereas normal cells under these conditions require embryonic juice as one of the necessary elements of maintenance. Another difference between tumor cells and normal cells has been found by Drew by this method. The delay required by adult tissues before starting growth under these conditions can be eliminated if an incubated kidney extract be added to it (Carrel's "Trephones"). An ice-cold kidney extract fails to accelerate growth; whereas an ice-cold tumor extract is just as efficient as the incubated kidney extract, the inference here being that malignant cells are constantly producing a growth-promoting substance which normal cells only produce when injured or autolyzed. The light that these observations throw on repair processes and a possible explanation of malignant transformation is considerable. By the tissue-culture method, also, Drew has shown that the loss of differentiation of cells, on which so much stress is laid by pathologists in tumor diagnosis, is a relatively superficial characteristic which in the case of epithelium can be removed *in vitro* by the admixture of connective tissue. By thus acquiring a base of operations, they revert to their normal form and habit of growth.

The important work of Maude Slye in the past thirteen years on hereditary factors in cancer incidence in mice must also be mentioned. By selective breeding, as is well known, she has secured in descendants of a limited, carefully selected stock, some strains that are practically completely resistant to cancer production and others that are unusually susceptible. The resistance to cancer seems to be a typical dominant character in the Mendelian sense, while susceptibility to cancer behaves as a Mendelian recessive. Although this is of course of extreme importance in comprehending the nature of cancer and applies equally well to man as a biological organism, it should perhaps be mentioned that it is of very little, if any, clinical significance, in the sense that the probability for cancerous offspring could be estimated in individual unions. In the necessarily mixed strains of human genetics, the conditions of the rat experiment will never be approximated, so that inheritance of cancer, cancer families and so forth will presumably continue to play a negligible clinical rôle.

Finally a few words about the parasitic theory of the cause of cancer, which has been maintained in one form or another since ancient times and is still not without upholders. Occasional increased local incidence of cancer in certain families, houses, streets or towns, or apparent epidemics in man or beast, have naturally given rise to speculation about its possible infectious qualities; but not only has proof of infection never been forthcoming in such cases, but they are often bristling with fallacies, and permit of other more logical explanations. The number of microorganisms which have been grown from cancer tissue and advertised as its cause is legion. Appearing from an early period in the history of bacteriology, even to the present day, none have stood the test of time, though some, such as Doyen's Micrococcus neoformans, were given considerable reclame and support. Spirochetae, blastomycetes, protozoa, mycetozoa have all been incriminated, but possible causes of error, such as technical or clinical contamination, production of tumor-like granulomata and not true neoplasms, the possibility of symbiosis or saprophytic existence and so forth, have always operated eventually to discredit any claims that have hitherto been made. Gaylord's thyroid tumor of fish is an entirely respectable example of this kind of error. Certainly our present knowledge of the natural history of cancer places a large burden of proof on anyone attempting to establish its parasitic cause. The most interesting recent experimental work on this line is Erwin Smith's elaborate investigation of the plant overgrowths caused by his Bacillus tumefaciens, easily isolated from crown gall. Even if it is accepted that he has produced true tumors, the reservation must be made that his bacillus may be acting like tar or arsenic or ova of nematodes or tapeworms, as what might be called a semi-specific irritant, i.e., an essential factor but not the cause of tumor growth, a consideration which is fortified by his ability to produce similar growths in plants by other means. Rous' filtrable chicken sarcoma and a few similar phenomena are still in the doubtful borderland. If proved to be a true neoplasm, our conceptions of tumor growths will certainly have to be modified to fit in with Rous' tumor.

I have tried to give a short survey of the various experimental methods that have proved of value in the study of the cancer problem. Not only have they intrinsic historical value, as examples of how the scientific mind has attacked a baffling complicated problem urgently set before it by the needs of the human race; but they are also practically valuable, as indicators of what to pursue and what to avoid and as possibly containing in one or other line the hidden solution of the problem of cancer.

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MAIMONIDES ON "PHYSICAL HYGIENE"

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Maimonides, the renowned Jewish physician and philosopher of the twelfth century, according to available records, wrote in addition to his various religious and educational works a number of treatises pertaining to medical topics. The range of subjects covered by him was exceedingly broad. Undoubtedly the most famous and best known of all is the "Treatise on Personal Hygiene,"[1] prepared for Alfadhel, the ailing son of Saladin, to whom he acted as personal physician. Almost equally as popular is his "Book on Poisons," written at the request of the Vizier Kahdi-el-Fadil.

Other of his titles include:[2] "Aphorisms From Various Medical Writers"; "Commentaries on Hippocrates"; "Compendium of Galen's Works"; "Translation of Avicenna"; "Etiology of Disease"; "Sanitary Regulations"; "Consultation on Various Accidents"; "Ethics"; and numerous writings on such topics as "Food"; "Medicaments"; "Hemorrhoids"; "Sexual Relations"; "Gout"; "Asthma"; "Physiology"; "Stomach" and "Brains." In addition there is his epic "Oath and Prayer for Physicians," which might well be placed along the side of the famous Hippocratic oath.[3]

It was through a desire to gain access to some of these writings that a small book entitled: "The Principles of Physical and Moral Health of Man," was obtained by courtesy of the Librarian of the Library of the Surgeon General of Washington, D.C. This work, consisting of forty-eight pages translated into French by M. Carcousse, and published in Algiers in 1887, is an extract of an abridgement of the Talmud which Maimonides prepared under the title: "The Second Law."

As epitomized in the introduction, the pages of the book "are full of truths, useful lessons, healthful advice, and gentle philos-