SCIENCE

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FURTHER EVIDENCE THAT CROWN GALL OF PLANTS IS CANCER[1]

TUMORS without visible cause are the subject of this address. They have been studied most numerously in man, but they occur also in the domestic animals, in wild animals (mammals, birds, batrachians, fish) and now, as we know, in plants. If this paper were given a full descriptive title it would read as follows: *Further Evidence that Crown Gall is Cancer, and that Cancer in Plants because of its Variable Form and its Bacterial Origin offers Strong Presumptive Evidence Both of the Parasitic Origin and of the Essential Unity of the Various Forms of Cancer Occurring in Man and Animals.* This is the text I shall talk to, and in passing I may add it is a view entirely opposed to the current views of cancer specialists.

To make plain what I have to say about plant tumors of this type it will be necessary briefly to mention similar animal tumors. This I shall do without special reference to medicine, *i. e.*, simply from the standpoint of a biologist, but first I shall show you the gross appearance of a few animal cancers. (Lantern slides.)

These tumors without visible cause are very common in man. They have been observed in every organ and in every tissue of every organ. They have been studied diligently by human pathologists, and especially by morphologists, for many years and there is now a great volume of literature respecting their structure and course of development, but very little is known as to

[1] Read before the Washington Academy of Sciences, May 11, 1916.

their cause,[2] and nothing as to the occurrence in them of any causal organism.

Clinically and morphologically they are divided into two well-marked groups—the benign tumors and the malignant tumors. All of these tumors, whether benign or malignant, are abnormal overgrowths (cellular proliferations) of the normal tissues of the body. Every organ and every tissue in which a benign tumor has been observed may also become the seat of a malignant tumor. Moreover, benign tumors sometimes behave like or become converted into malignant tumors. Often, in early stages of growth it can not be foretold whether a given tumor will continue benign or become malignant. Benign tumors are, therefore, always to be considered as a possible source of danger, and their interrelations, if any, with cancers can not be known until their causes are known.

As a rule, benign tumors grow slowly, although often eventually they reach a very large size, exceptionally weighing more than the rest of the body. The cells composing them approximate in form, and in size (that is in maturity), the cells of the normal tissues. Owing apparently to their slow growth, there is also a body-reaction in the form of an enveloping capsule, which shuts off the tumor from the surrounding tissues. These tumors are called "benign" because while they often cause great inconvenience and sometimes death, they are restricted, usually, to the locality where they first appear. That is, they do not develop destructive daughter tumors in other parts of the body.

On the contrary, the cancers, or malignant tumors, with a few exceptions, produce daughter tumors freely (often in vital organs), grow rapidly, are destitute of a restraining capsule, *i. e.*, become invasive, and are composed of cells, which, while showing all grades of transition, are often much smaller and more embryonic in their appearance than cells of the tissue from which they have originated, and are then most malignant. These immature cells are readily distinguished, however, from normal embryonic cells both by their disturbed polarity and by their reaction to stains. In other words, they are not genuine embryonic tissue, because they do not possess either the full structure or the entire capability of embryonic tissue. These cancer cells proliferate freely, sometimes with astonishing rapidity, invade and destroy normal tissues, and in various ways act like a foreign organism, that is, they behave in the manner of a parasite, although they are a part of the body.

Without including all of the forms known, or going into a swamping multiplicity of details, I may say that the cancers, or malignant tumors, may be subdivided into four principal groups: (1) The sarcomas, which are malignant fleshy proliferations of the various types of connective tissue; (2) the cancers proper, or carcinomas (including the epitheliomas) which are destructive (eroding) proliferations of the epithelium of the skin, mucous membrane, and glandular tissues generally; (3) the so-called mixed tumors containing proliferating elements from two germ layers, *e. g.*, the chondro-sarcomas composed of proliferating cartilage and connective tissue, the adeno-sarcomas composed of glandular tissue and connective tissue, etc.; and (4) the embryonal teratomas which, in addition to the cancerous element that is often a sarcoma, contain teratoid elements representing all three germ layers—young

[2] Dass das Dunkel auf diesem Gebiete noch nicht erhellt, des Rätsels Lösung noch nicht gefunden, das zeigt die noch stetig zunehmende Fehde der Streiter auf diesem Felde. Hie embryonaler Keim, hie parasitärer Ursprung, hie Metaplasie, hie Anaplasie, hie Anarchie, so lauten die Schlagworte der Autoren (Wilms).

tissues of various organs, frequently an astonishing mixture of teratoid elements, but all embryonic. These are also known as *atypical teratoids* in distinction from *monsters,* which are pre-natal malformations, and from *typical* (ripe or adult) *teratoids* which also are not cancers, but growths due to pre-natal disturbances, the commonest form of which is the ovarian dermoid. By Wilms they are called solid embryomas or embryoid tumors in distinction from the typical teratoids, which he calls cystic embryomas or simply embryomas.

The atypical teratoids grow rapidly, metastasize freely and are commonest in the early decades of life. In the typical teratoids the fetal fragments have grown with the growth of the host. Although dwarfed, they are as old as the individual out of which they have come, *i. e.,* they contain old skin, old teeth, old bones, long hair, etc. In the atypical teratoids the fetal fragments are always very embryonic and probably are never more than a few months old, or a few years old, no matter how old the person from whom they have been removed, *i. e.,* growth goes on in them independently of the host. Moreover, these atypical teratoids always contain cancerous elements. It is this latter type of tumor that I have recently produced in plants.

In the benign tumors, to return to animals, the tissues are arranged in a nearly or quite normal fashion and the cells are full grown, only much more abundant than they should be. In the malignant tumors the tissues are not only more embryonic, but are arranged atypically, the cells having lost a part or the whole of their polarity, *i. e.,* their orderly arrangement. Frequently, they also show defective mitosis, and very frequently polynuclear cells (the so-called "giant cells") appear, owing to fission and fragmentation of the nucleus without any corresponding cell division. Lobed and cleft nuclei are very common in cancers. They are also common in crown gall.

Cancers in addition to the malignant cells contain a stroma or framework of connective tissue and a system of blood vessels and lymph channels by means of which they are nourished, but the blood flow in these vessels is not controlled by any vasomotor nervous system. Ordinarily cancers do not contain any nerves, the associated pain being due to pressure on outside nerves.

All of these tumors are imperfectly provided with blood vessels and are subject to early decay, the resulting cavities, or open wounds, being exposed to various harmful secondary infections. In early stages of growth these tumors are purely local and may be removed surgically with good prospect that they will not return. In late stages these tumors exert a markedly detrimental effect on the whole body, which is visible as atrophy, anemia and cancerous cachexia, and surgical interference is then of little or no avail.

The daughter tumors are produced from the mother tumor in several ways, *i. e.,* by contact of a diseased area with a healthy area, as for example, by tongue against lips, or cheek against jaw; by invasive growth, *i. e.,* tumor-strands out of which the secondary tumors develop as in cancer of the breast; by motile (creeping) tumor cells; or finally, by cells or fragments dislodged by the blood stream or the lymph stream and carried to distant parts, where they multiply. The carcinomas usually invade by way of the lymphatics; the sarcomas and the embryomas, by way of the blood-vessels. When a tumor-strand can be traced from the daughter tumors back to the mother tumor they are called *invasive growths;* when no such connecting link is

visible they are called *metastatic* (or shifting) *growths*. Some modern writers, however, use the word metastasis for a daughter tumor of any origin.

As I have said, nothing is known respecting the cause of these human tumors and the great majority of cancer workers have come to the conclusion (which I believe is erroneous) that they can not be due to parasites.

It is well here to pass in review some of the objections to a parasitic theory of cancer: (1) Because many authors of distinguished reputation (Ribbert, for example) maintain that they are insuperable; (2) because so long as they are not met various persons will be discouraged from undertaking active researches designed to uncover the parasite; and (3) because, finally, if I can convince you that crown gall is a cancer, you will then be ready to admit that what requires a schizomycete for its production in the plant is not likely to be produced in any very different way in man and animals. Here then are some of the objections, and I will meet them as fairly as I can.

1. Nothing definite in the way of a parasite has been made out by use of the microscope. *Answer:* This is admitted, but it proves nothing. If we exclude the Negri bodies, still in dispute, the same is true for rabies. And in cancer we have the Plimmer bodies and other cell-inclusions of a doubtful nature, some of which may be bacterial or protozoan. The etiology of crown gall would still be in doubt if we had depended solely on the microscope, for no ordinary staining will demonstrate a bacterium in the cells, and yet it is there. For the final analysis recourse must be had to cultures and inoculations. There are then some problems in pathology which never can be solved simply by the use of the microscope.

2. From cancer no parasite has been isolated in spite of diligent bacteriological search. Innumerable cultures have been made and many inoculations and all have failed. *Answer:* The same is true of yellow fever. No parasite has been found. Until recently the same was true of syphilis. Ten years ago it was true of crown gall. There may be some very special reason (as in crown gall, or in certain types of arthritis) why isolations have failed; or the right organism may have been isolated and inoculations may have failed simply because the inoculated animals were *normal, i. e.,* fully protected by their leucocytes and therefore not susceptible. We must, I think, conceive of cancer as developing only in a weakened, unprotected condition of the body. The more or less ready growth of grafted cancer in certain animals offers no real contradiction because here the conditions are somewhat different from what they would be in case of a naked bacterial inoculation, because the grafted cancer cells are autochthonous cells and are introduced into the mouse or other experimental animal in a considerable compact mass, the inner cells shielded by the outer ones and all developing a kind of protective aura under the influence of which union with the host tissues takes place and the cancerous growth continues.

3. Heredity is a sufficient explanation. *Answer:* The same thing was said repeatedly of tuberculosis prior to 1884. Now we see that heredity furnished the canvas but could not paint the picture. Miss Maude Slye's work on heredity of cancer in mice is astonishing and praiseworthy, but I do not feel sure that a similar picture could not be obtained by breeding together tuberculous animals, indeed I am quite certain that the results of such experiments would be a vastly increased number of tubercular animals, and if we knew no more about the cause of tuberculosis than we do about the

cause of cancer, the interpretation of the results would be entirely wrong, *i. e.,* they would be ascribed wholly to heredity, whereas we know that two factors are involved: (1) heredity; (2) infection. I do not think Miss Slye has established the fact that cancer follows Mendel's law.

4. There is no need to postulate any parasite, since the cancer cell itself is the all-sufficient parasite and no cancers can be produced in the absence of this cell. *Answer:* It is strange that the authors of this statement, which has been dinned into us for a generation, can not see that it is no answer at all, but only a makeshift. As well say: Tetanus is due to tetanin. Certainly, we all admit this, but what originates the tetanin? and what originates the cancer cell? Moreover, loath as these objectors are to admit it, cancers (sarcomas) in barnyard fowls can now be induced by cancerous material all the cells of which have been removed by *filtration,* or have been killed by *heat,* by *freezing,* or by *drying* (Rous). And how should anemias and cachexias arise as the simple result of the proliferation of body cells? In other diseases they are the direct result of bacterial or protozoan multiplication in the body. In this connection reflect for a moment on what goes on in streptococcal arthritis, in persistent agues, or in yellow fever and in blackwater fever where the red blood corpuscles are destroyed wholesale. Even pernicious anemia will, I believe, be traced eventually to a blood-destroying parasite. All that we yet know definitely concerning the natural occurrence of anemias (I am purposely excluding surgical ones) is that in certain diseases they are due to blood-destroying parasites, and it is not going very far afield to assume that anemia is so produced in cancer.

5. The idea of a parasite is too complex. We know that we can graft cancer only within the narrowest limits, and also that within the same species each sort of cancer reproduces its own kind. We must therefore postulate not only as many different cancer parasites as there are animals subject to cancer, and that is probably every kind of animal, but also a parasite for every special kind of cancer in each particular animal, which is a *reductio ad absurdum. Answer:* This is a molehill magnified into a mountain—an unsubstantiated and unwarranted hypothesis! The history of science is full of such objections. Against the plainest evidence it is always easy for certain types of mind to raise objections, which then generally are left to some one else laboriously to test out experimentally, whereupon they vanish into thin air, the objections not having been well grounded. Some people are good *only* as objectors! They can not do anything concrete. It is less than twenty years since certain theoretical Germans were saying: There are no bacterial diseases of plants and can not be any, for the reasons we have given. Yet the experimental method has demonstrated the existence of nearly a hundred. In science, no theory is worth a picayune that does not have an experimental basis under it! There have been at least thirty so-called explanations of cancer origin propounded during the last half century, not one of which really explains or has any experimental basis under it. Cohnheim's theory is one of these; Ribbert's is another.

From the behavior of the cells of one species when grafted on another species we can postulate nothing as to what a naked microorganism would do under the same circumstances. As a matter of fact, plants also can not be grafted widely, yet the crown-gall organism is widely inoculable. *Moreover, it yields one result when inoculated into one set of tissues and a different result when inoculated into another set of*

tissues. In malignant neoplasms in man, and the lower animals, why then may we not assume for experimental purposes an intracellular parasite capable of producing sarcoma when infecting connective tissue cells and other types of tumor when infecting other tissues—each tissue presumptively developing according to its own type? Theoretically I can see no objection to this view, and actually we have this very thing occurring in crown gall.

6. Parasites destroy cells. They do not cause them to proliferate, and calling cancer a cell-symbiosis does not help matters. *Answer:* The world progresses and new knowledge modifies or supplants the old. Menetrier, of Paris, without knowing anything about our experimental work on crown gall, and being very sceptical as to the parasitic origin of cancer, saw clearly in 1908 (and so stated in his book) that there was no objection theoretically to assuming that in cancer there might be a parasite which did not destroy cells, but continually stimulated them to divide, only he said: What is the use of speculating, since nobody has shown any concrete example? This may have been true of that time, but it is no longer true, since there is just such a cell-parasite, or cell-symbiont, in crown gall.

7. In cancer, portions of the body grow in places where they should not, having come to the place by growth-extension from the primary tumor or having been transported there by a blood stream or a lymph stream. Nothing like this occurs in any parasitic disease. *Answer:* Formerly this statement corresponded to our knowledge, but now it does not, because just this thing occurs in the parasitic plant disease of which I am speaking, viz., invasion or growth-extension from a primary tumor resulting in the occurrence of secondary tumors in what previously were normal parts of the plant!

8. Direct stimulation of cell growth by a parasite is an unknown occurrence in biology. In all cases in which parasites are found within cells the effect is the destruction either of the parasite or of the cell. *Answer:* Antiquated information. True of many things, but not of *all.* Theoretically a third possibility exists, and actually we have it in crown gall. Here the parasitized cells are not destroyed, neither are all of the bacteria within them killed, but only most of them. There is a very delicate balance between the two, which results not in death of the host cells, but in an increased tendency to cell-division, a tendency strong enough to overcome the physiological control of the plant. When death results it is not due to the direct action of the bacteria, but to other factors, *e. g.,* nutritional defects, and secondary parasitisms.

9. Since cell proliferation in tumors is similar to cell proliferation under normal conditions, the assumption of a parasite to explain it is quite unnecessary, and makes an explanation of tumor-growth more difficult. *Answer:* Similar is not necessarily *the same.* Conclusions drawn from cultures *in vitro* do not necessarily apply to growth within the body. Cell-proliferation of tumor tissues in the body is similar, of course, to normal cell proliferation, *but with a difference,* namely, in the tumor there is an *unknown something,* which compels these cells to proliferate *in opposition to the needs of the body and in spite of the physiological body control.* Surely something very foreign to the body is required to explain the *undifferentiation,* anaplasia we call it, following von Hansemann, and the *excessive vegetative force* of the cancer cells. Moreover, so far as it is able to do so, the body treats individual cancer cells, or groups of cancer cells (metastatic fragments) exactly like parasites, that is, it envelops them in a blood clot and destroys them. In cancer, therefore, considering

what takes place in crown gall, I think we are warranted in searching for an intracellular parasite, probably some common organism, as the unknown factor, necessary to satisfy the equation and explain the phenomena. Moreover, I fail to see how the assumption of a parasite makes the explanation of tumor growth "more difficult." These objectors are here dealing with one of their many *assumptions* while I am dealing with *a fact*. I insert my infected needle and I obtain a tumor. I insert a sterile needle and the wound heals normally. Into one branch of a young Paris daisy I set my infected needle 50 times and obtained 50 tumors; at the same time into the twin branch I set a sterile needle 50 times and obtained no tumors whatsoever, but only a normal healing of the wounds. Cell proliferation *per se* in no way explains cancer. Normal cells, also, judging from the way they behave in blood serum under the microscope, must often proliferate into the plasma of the body, but such wandering cells are promptly disposed of in accordance with the law of antagonism or of physiological control, or whatever you please to call it. I mean the action of the body as a whole. Otherwise, we should have occurring continually in the body what takes place when normal tissues are cultivated *in vitro*, that is, a copious cell proliferation, which would be disastrous. This we do have in cancer, but since cancer develops in opposition to all the compelling forces of the animal body it must be owing to a profound disturbance of the normal (interior) activities of the cells involved. What is so likely as a microorganism to produce this cell disturbance leading to the formation of a tumor? Especially what, since in the plant we know that one does produce just that?

10. Cancers are due to long-continued inflammatory conditions. They begin in bruises, in old (unhealed) wounds, X-ray burns, charcoal stove burns (Kangri cancer), and various irritations and injuries incident to special trades (chimney sweeps' cancer, paraffin workers' cancer, etc.). *Answer:* The second statement is admitted. They begin in all of these places. The first statement is a *non sequitur*, a *post hoc ergo propter hoc* argument. Wounds are often infected with visible parasites, why not sometimes with invisible ones? Not all irritations end in cancers. Of two long-continued irritations one may become malignant and the other not. This is wholly inexplicable on the theory of simple irritation, but readily interpreted if we assume that cancer is due to a special and unusual kind of parasite, certain long-continued irritations having paved the way for a peculiar infection by having reduced the resistance of the body.

11. Surgeons, nurses and relatives do not contract cancer. It therefore does not behave like a communicable disease. *Answer:* Neither does malarial fever; neither does arthritis; neither does leprosy; and, finally, neither does crown gall. We must recognize that in nature there are all grades of parasitism and must be prepared to welcome forms not hitherto recognized. In pathology, as everywhere else, the open mind is after all the best asset. Closed and crystallized minds are of no further use in the world! Certainly cancer is not an acute infection, and no one regards it as such. It may be due, however, to a parasite, visible or invisible as the case may be, *some feeble parasite against which the normal body is fully protected*, some common organism, living saprophytically on the body, or in the soil, able only to infect a depleted body, and destructive only when through wounds (very slight ones, it may be) it has penetrated into the interior of certain cells, which neither kill it nor are killed by it, but

where it depresses functional activity while at the same time enormously stimulating vegetative activity. In the present state of our knowledge no one can say that this is an untenable working hypothesis. Indeed the probabilities in favor of such a view are much stronger to-day than they were five years ago, when I first discovered the cancerous nature of crown gall and began to formulate my ideas.

12. We might, possibly, concede sarcomas to be due to a parasite, but not carcinomas, and certainly not embryomas, yet whoever proposes a parasitic theory of cancer must not only demonstrate his parasite but with it must account for all of these diverse forms, and especially for embryomas, since they are the crux of the whole situation.[3] *Answer:* This is admitted. All of these forms hang together, and the claim is now made that embryonal teratomas and gland proliferations can be induced with the same schizomycete previously used to produce sarcomas. As a negation it is of no consequence whatever to say that I have only produced them in *plants,* because, little as it is yet recognized, plants are better adapted than animals to certain purposes of cancer research. In due time and in the same way, let no one doubt, they will also be produced in animals. *Whatever else may be denied, the bold fact now stands out demonstrably that all the leading types of cancerous proliferation can be produced in plants with one microorganism.* If any one doubts it, let him repeat my experiments.

13. But this hypothesis of the origin of cancers, and especially of embryonal teratomas upsets Cohnheim's theory of "cell-rests." *Answer:* It does, beyond doubt, very completely. But there is no use of making a fetish of Cohnheim's theory. It is, after all, *only a theory.* It seemed once to furnish the basis for an explanation of cancer origin, but no one was ever able to build a superstructure on it, for no one can explain why some "cell-rests" grow into cancers while others, and by far the larger number, remain dormant. We shall simply have to write *Hic jacet* over Cohnheim's theory. It serves well enough for monsters and for typical teratoids, but it does not explain cancers.

14. Plants are so unlike animals that no comparison can be drawn from diseases of the one group to those of the other group. *Answer:* On the contrary, fundamentally, plants and animals are very much alike. I mean the resemblances are much more basic than the differences. The latter, very conspicuous to the eye, may be regarded as differences of degree rather than of kind, corresponding to differences in function. Such an objection could never be raised by a biologist. It shows perhaps better than any other argument how great is the need of injecting biological concepts into cancer research. The cancer problem would have been settled long ago, I believe, had it been approached commonly from this angle rather than from that of pure morphology. Of many of the lower forms of life it is still very difficult to say whether they are plants or animals, of the whole group of bacteria, for example; and for the primitive, doubtful forms of life you will recall that Haeckel created the special kingdom of Protista. To my mind a fundamental unity runs through all living things from the lowest to the highest, like the gold thread through a tapestry! For one thing, all are *alive;* all possessed of that unstable equilibrium of forces expressed by the words *growth* and *decay.* These phenom-

[3] Gerade in diesem Punkt scheint mir die interessanteste und wichtigste Beziehung der Teratomen zu den anderen Geschwülsten zu liegen, dasz wir in den Teratomen eine Gruppe von Produkten vor uns haben, in welcher sich die Hauptfragen der Geschwulstlehre wie in einen Brennpunkt vereinigen (Borst).

ena are the properties of a substance called *protoplasm.* In both plants and animals this substance is organized into the form of cells. In both, usually, it is the outer protoplasmic membrane that controls the passage of *ions,* the disassociated electrically charged elements of water and other compounds. The same wonderful process of cell-multiplication by *mitosis* occurs in both plants and animals. In both, except in the lowest forms, these cells are organized into *tissues,* with *division of labor.* In both there is a *sexual method of reproduction.* Plants, indeed, propagate also *non-sexually by budding,* but so do many of the lower animals. In many plants there is *regeneration* when parts are cut away, but so there is in a great variety of animals. Even their foods are not different. It is true, the plant differs decidedly from the animal in possessing an apparatus for elaborating inorganic substances into starch, sugar and proteids which the animal consumes, but it makes these substances for its own use, not for the animal. It is sometimes assumed that the inorganic substances, of earth, air and water, are the food of the plant, but such is not the case. The plant depends for its growth on the same nutrient substances as the herbivorous animals, viz., on starch, sugar and proteids, which it has stored in every seed and under every growing bud. The phenomena of birth, growth and decay are essentially the same in plants and in animals; but corresponding to higher development, the animal has many special organs either wanting altogether in the plant, or greatly simplified; it also has flexible cell-walls while the plant has rigid cell-walls; but both plants and animals *respire;* both *assimilate* food substance, and *oxidize* them with resultant work; both require about the same amount of *water and mineral salts;* both have a *circulation* of fluids; and both *secrete* and *excrete* a variety of substances, acid, alkaline and neutral. The *response to stimuli,* such as gravity, heat, light, radium, X-ray, electricity and poisons, is much the same in both groups. In irritable response plants and animals both obey Weber's law (called also Fechner's law and the psycho-physic law), that is, to increase a response in an arithmetical ratio the stimulus must be applied in a geometrical ratio. There is a suggestion, even, of a nervous system in plants since stimuli are passed along certain channels to distant organs and the movement can be slowed down by cold, increased by heat or inhibited by poisons applied midway, the response, according to Bose, being not simply hydro-mechanical. Even the idea of locomotion does not distinguish animals from plants. Many of the lower animals are rooted fast, while many of the lower plants have swimming organs and are actively motile. Moreover, all of the higher plants change position more or less; all are sensitive; all show rhythmic movements. Finally, the *intimate cell-chemistry* of the two groups (production of digestive enzymes, amino acids, etc.), so far as known, is much alike. There is no *a priori* reason, therefore, why a special stimulus to cell division in plants might not prove to be of the highest interest to students of cancer in man and the lower animals. It is a matter to be taken up like any other and tested out. Researches on crown gall should have been undertaken long ago in every cancer laboratory in the world and would have been had we not unfortunately discovered a parasite. That killed the whole subject in the eyes of the orthodox! Not having found a parasite themselves, they will not believe that any one else can do it, or that there is one; and this in spite of the fact that the history of parasitic diseases from Pasteur's time down shows clearly

enough that the folly of one generation has been the wisdom of the next!

Von Hansemann has said[4] that crown gall has nothing in common with cancer except its name (Krebs). I am quite willing to let specialists weigh my evidence and decide for themselves, if only they will wake up and begin to do so! not simply ignore the whole subject because it comes to them from an unusual quarter, and is "too botanical," as another German editor said in refusing one of my papers.

In his "Principles of Pathology"[5] Doctor Adami gives the following as the characteristics of the atypical (malignant) tumors: (1) Vegetative (embryonic) character of the tumor cells; (2) rapidity of growth; (3) peripheral extension, lack of capsule and infiltration of the surrounding tissues; (4) tendency to develop metastases; (5) tendency to central degenerative changes; (6) liability to recurrence after removal; (7) cachexia; (8) anemia. All of these occur in crown gall except 4 and 8. There is nothing in the plant corresponding to blood, and the rigid cell-wall of the plant prevents metastasis in the true sense of that word. But if we use metastasis in Ribbert's loose way, then metastasis also occurs in crown gall.

One of the striking things about cancer and one separating it off sharply from all other animal diseases, is the fact that the secondary tumors are not granulomatous proliferations. That is, the secondary tumors are not a growth-response of local tissues to an irritation, and hence are not comparable to the protective granulations formed in the healing of a wound or in such a disease as tuberculosis, but they are due to the migration from the initial tumor either of infected cells or of deteriorated cells which continually reproduce their own kind to the detriment of all others. The cancer cell is a lawless entity, different in its tendencies and capabilities from any other cell of the body, and so far as we know, it always reproduces its kind, the daughter cells being cancer cells and not normal cells. Why this is so is wholly unknown in human and animal pathology, but that it is so admits of no doubt whatever. To illustrate: If medical men were able to reach into the center of tubercle nodules or syphilitic nodules in the human body, and kill the nest of pathogenic bacteria in the one case and of pathogenic protozoa in the other case, without injuring the unparasitized barrier cells forming the periphery of these nodules, then these cells would be immediately destroyed and removed from the body as no longer of use, or else would behave once more as normal body cells (scar tissue). In cancer, on the contrary, as every surgeon knows, if any cancer cells are left after an operation—even the least number—they are likely to reproduce their evil kind, in which case another tumor results either in the old locality or in some other part of the body. In other words, the outermost cancer cells are not barricades erected by the body to prevent further encroachments of the enemy, but are self-multiplying outposts of the enemy himself. However, this does not militate against the belief that some of the elements in a malignant tumor are harmless ones.

Very few laymen, I believe, have any clear conception of the exact mechanism of the cancerous process, and not a few physicians also seem to be ignorant of it. Cancers are the result of the multiplication in the body of certain body cells which have become abnormal and dangerous to the rest of the body, or as we say "cancerous," a single cell or a few cells to begin with, then

[4] *Zeitschrift für Krebsforschung*, 12te Bd., 1913, p. 146.

[5] Vol. I., p. 671.

many. Whether infected or only degenerate, these cells retain their hereditary tendencies, that is, liver cells to reproduce liver; brain cells, brain; connective tissue cells, connective tissue; and so on; but all of them while deriving nourishment from the body have become more or less emancipated from body control and exercise their freedom by an unlimited and hasty multiplication very destructive to the other tissues of the body. They reproduce their kind first in the primary tumor and later in secondary tumors. I can make this plainer perhaps by another illustration. Following tuberculosis of the lungs there sometimes occurs blood-infection and a generalized tuberculosis of every organ in the body, but in such cases the nodules wherever they arise are due to local bacterial irritation, and are always built up out of local tissues, liver tissue in the liver, spleen tissue in the spleen, and so on. In cancer, on the contrary, it is the cancer cell which migrates with all its hereditary tendencies and the secondary tumor, therefore, reproduces more or less perfectly (or imperfectly) the hereditary cell complex of the primary tumor, so that the trained pathologist after studying sections of a cancer can usually (but not always) decide whether it is primary in the organ under examination, or secondary, and if secondary, then in what other organ the primary tumor is to be sought. For example, if a primary cancer occurs in the liver and there are metastases to the lungs the *lung tumors will contain liver cells;* so if a primary cancer occurs in the stomach and there is metastasis to the liver, the liver tumor will not be formed out of liver cells *but out of stomach cells.* It is a very striking thing to see under the microscope, particularly in a well-stained section, a nest of malignant glandular stomach cells in the midst of a piece of liver. I do not know that it has been actually proved but undoubtedly such a liver tumor must have the power of secreting pepsin or at least of mucin, just as we know that metastases from a primary liver tumor into other organs may retain the power of secreting bile.

I have now come to another way in which these plant tumors resemble cancer in man and the lower animals, viz., in the striking fact that as in animals the secondary tumors reproduce the structure of the primary tumor. Thus, when a primary tumor is induced on a daisy stem by inoculation, deep-seated secondary tumors, developed from parenchymatic tumor-strands, often arise in the leaves and these tumors convert the unilateral leaf or some portion of it into the concentric closed structure of a stem. (Slides shown.)

Having now reviewed my older discoveries,[6] I come to details of more recent ones also bearing directly, I believe, on the etiology of cancer.

I have referred to the rapid growth and early decay of cancers in men and to the common occurrence of atrophy and cachexia in connection with such tumors. Similar phenomena occur in the plant. I show you three slides from photographs of galled sugar beets. They were grown in different years (1907, 1913 and 1916) but each showed the same thing, viz., sound control plants and dwarfed, sickly (yellow) and dying inoculated plants. Each inoculated plant bore a tumor larger than itself and the time from inoculation to date of the photograph varied from 2½ to 4⅕ months. This year I have obtained the same results on ornamental (white flowered) tobacco. At the end of five months all of these inoculated tobaccoes are dead or dying from large tumors of the crown, whereas the control plants are healthy, many times larger

[6] See this journal, N. S., Vol. XXXV., p. 161.

and now in blossom. To get such prompt, disastrous results, the inoculation must be fairly early in the life of the plant and near the growing point.

Secondary infections due to other organisms are also as common and as disastrous in crown gall as in cancer in man. Just now in the hothouses we have striking examples of it on the Paris daisy and I will show you a few slides. (Slides.) These secondary infections may be either fungous or bacterial.

Third, let me show you some examples of *infiltration,* taken from sunflower heads inoculated last year. The first three slides show hard greenish gray vascular tumors which have developed from a few needle pricks made into the extremely vascular thin layer which bears the seeds. The one shown in vertical section is from the middle of the flower disk and it has grown downward in the white pith for a distance of 4 inches. It lies in the pith but has not developed out of pith. The fourth slide from another tumor shows cancerous cells and vessels of the supporting stroma pushing out into the sound tissues much as roots do into a fertile soil. The fifth slide is from the cortical part of a teratoma on *Pelargonium.* Here the small-celled blastomous tissue has crowded in between coarse cells of the cortex.

Next to be considered are examples of atypical blastomous tissue taken from different parts of the same tumor (a young deep inoculation into the stem of a Paris daisy). In the first slide, at the left, is a part of the supporting stroma (cortex cells); the right side shows round cells of the same type that have become cancerous, *i. e.,* much smaller, more embryonic, rapidly proliferating, large-nucleate and deep-staining cells which have lost their polarity. The second slide shows spindle-shaped blastomous cells from the outer part of the same tumor. This tumor is the ordinary rough gall of the daisy stem, which is a sarcoma as near as the plant can make one, that is, a sarcoma minus the intercellular fibrils which are wanting in plants.

Now let us consider how plastic the living tissues can be when they are brought under a cancer stimulus. I show you photomicrographs of tumors (atypical hyperplasias) produced by inoculating the crown-gall organism into the extreme outer bark (living cortex) of young stems of Paris daisy, the inoculated cells being ordinary cortex cells. These tumor cells which conceal the bacteria (there are none in the intercellular spaces) have become more embryonic than the tissue out of which they have grown. This is shown by their size ($\frac{1}{20}$ that of the cells from which they have developed), their large nuclei and their avidity for stains, as well as by the peculiar way in which they fix the stains. It is also shown by the fact that they can produce vessels in their midst (trachei) whereas the uninjured cortex never produces vessels. The embryonic tissues of the plant, however, have this vessel-producing power. In a word, these tumor cells have become more embryonic than the tissue out of which they have developed and have lost their polarity, and this is exactly what occurs in cancer in man, as I shall show you. I have produced these superficial fine-celled hyperplasias out of coarse-celled cortex, not once, but a number of times, and in several different kinds of plants.

Thus far I have spoken only of one type of tumor, the common crown gall. Until this winter (if we except hairy root) I did not know of the existence of other types. Now I believe from what I have seen that all the leading types of cancer, viz., (1) sarcoma, (2) carcinoma, (3) mixed tumors and (4) embryomas, occur in plants and that all are due to one and the same organ-

ism. I certainly have abundant material of the end terms (Numbers 1 and 4), and enough of 2 and 3 to convince myself, if not others.

The "further evidence" alluded to in the title of this paper relates more especially to the embryomas and consists of the discovery of an entirely new type of plant tumor due to the crown-gall organism, in which tumor there are not only ordinary cancerous cells of the common crown-gall type but also entire young shoots or jumbled and fused fragments of leafy shoots and of other young organs, thus making the tumor correspond to the highest type of animal cancer, in which in addition to the blastomous element there are fragments of various fetal tissues, sometimes representing many organs of the body. This is, I believe, the first time this type of tumor has been produced experimentally, and it has been done with the bacterial organism cultured from an ordinary rough crown gall of the simpler, well-known type. It was first done by inoculating the leaf axils of growing plants, *i. e.*, the vicinity of dormant buds, in other words, centers containing totipotent cells. Some of these strange tumors have produced daughter tumors in other parts of the stem and in leaves and, as in the embryonal teratomata in man, a portion of these secondary tumors have the full structure of the primary tumor.

I have also produced these teratoid tumors in parts of plants where no totipotent cells are known to exist, but only young plastic cells normal to the parts and hitherto supposed to be able to produce only one kind of organ. This will be plainer if I say that by needle pricks introducing the bacteria locally I can now produce atypical teratoid tumors in internodes and in the middle of leaves, an astonishing discovery, and one bound, I believe, to revolutionize our views as to the origin of these tumors in man. I do not here deny that totipotent cells, hitherto unsuspected, occur in the places I have inoculated, indeed they must so occur, but I only cast doubt on their abnormal occurrence in such places, *i. e.*, as the result of early embryonic dislocations.

The belief that I have also produced "mixed tumors," that is, tumors containing distinct types of tumor cells originating from different layers of the plant, rests on stained sections of tumors from several different kinds of plants. The evidence here is not as complete as in the case of the embryonal teratoma, and I am still experimenting. What I think I have in one part of the tumor is sarcoma originating from the deeper connective tissue layers and in another part of the tumor carcinoma derived from the skin and glands of the plant. However this may be, it is now beyond question that two very distinct types of plant tumor (sarcoma and embryonal teratoma) corresponding to similar types in man, as nearly as plant tissues are able, can now be produced by bacterial inoculations, *using the same organism.* To get one type of tumor I inoculate one set of tissues, and to get the other type, another set of tissues.

Coming to the details of my newer studies, I shall first take up the question of the possible existence of carcinoma in plants, the slides I shall show you being from photomicrographs of what I consider to be "mixed tumors." All are due to pure-culture inoculations, but they show a diverse internal structure suggestive of a mixture of epithelioma (skin cancer) and sarcoma (connective tissue cancer). There is still, perhaps, some doubt as to the interpretation of these facts, so that I speak only with reserve.

The first slide I show you is from a teratoma on the common *Pelargonium* or house

geranium, but in this connection I invite your attention only to a small portion of its surface (teratoid part) where strange phenomena are in progress, quite like what often occurs in the epithelium of human teratoids. Here is a compact, small, surface tumor showing subepidermal erosion, an effort on the part of the plant to protect itself. Its deeper tissues fuse into those of the epidermis in such a way as to suggest that they have originated from the latter, *i. e.*, there are no epidermal and subepidermal differences, although these differences are conspicuous in the normal plant and also in other parts of the teratoma. In this late stage of development it is impossible to tell what may have been the origin of these queer tumors, but what appear to be much earlier stages of the tumor are visible in several places, especially on their margins, and these places exhibit, or seem to exhibit, all stages of transition between the normal one-layered faint-staining columnar epidermis (equivalent to an epithelium), and a several-layered, large nucleate, loosely arranged, deep-staining tissue, the cells of which are rounded or angular and have lost their polarity, that is, their orderly relation to their fellows. Now this is exactly what takes place in early stages of carcinoma. For instance, below the one-layered epithelium in glandular tissues of the breast, of the stomach, etc., irregularly placed, large, deep-staining, rapidly proliferating cells make their appearance as shown on the next slide, which is from a cancer of the lung. This kind of proliferation is recognized as the beginning of a malignant tumor, and surgeons base their operations on its presence or absence. If, in the breast, let us say, this displacement of cells is present, then the surgeon does a major operation, but if it is not present, then he is content with having removed only the local nodule. These surface tumors on the geranium were accidental discoveries, but I have now begun a systematic inoculation of the skins of plants to see what I can get.

I have what I believe to be the same phenomenon (a mixed tumor) on tobacco. This tumor I produced out of young cortex in 1907, but it has been properly stained and critically studied only recently. Its outer part consists of blastomous cells quite different in shape and staining capacity from the cells of its inner part. The outer cells are more or less compact and angular and the protoplasmic contents stains uniformly. The inner cells are round, more loosely arranged and stain like the ordinary sarcoma cells of this tumor. In connection with the last slide I would also call special attention to the evidence it shows of the appositional transformation of normal cells into cancer cells (atypical blastomous cells). I refer to the band of tissue lying between the normal cortex on the right (out of which the tumor has developed), and the fine-celled hyperplasia on the left. These 10 or 12 rows of cells, bordering the tumor, have the same arrangement as the tumor cells and stain deeply like those of the tumor, but are several times as large. Occasionally an unchanged cortex cell is buried in their midst. They are, I believe, a transition from the normal tissue into cancerous tissue.[7] The same phenomenon has been seen in human cancers by several good observers and there can be no doubt as to its occurrence.

Finally, from shallow bacterial inoculations done on the glands of *Ricinus* last winter I have also obtained what appears to me to be satisfactory evidence of glandular proliferations, *i. e.*, rapid multiplication of the surface layer of cells with loss of form and polarity and entrance into the

[7] See *The Journal of Cancer Research*, April, 1916, Pl. XXIII., Fig. 78.

subepidermal region as an invasive hyperplasia. The punctures were deep enough, however, to have infected the subglandular connective tissue which is also proliferating. The sections were cut at the end of 27 days and show transitions from a columnar (glandular) epidermis into an irregular, angular-celled, large nucleate, deep-staining mass of rapidly multiplying atypical cells corresponding to an epithelioma (slides). The shape of these cells is exactly that of proliferating epidermal cells from my 1/100 mm. deep 72-hour inoculations on tobacco stems. I have not yet obtained metastases from such surface growths, but I am only now beginning my studies of skin and gland proliferation and there is much to learn.

We now come to embryomas. Before describing the atypical teratoid tumors I wish to make some general remarks. Conceiving human and animal cancer to be due to a parasite, I have been greatly interested for the past ten years to see to what extent the phenomena of such cancers, the cause of which is unknown, can be paralleled by crown gall phenomena the cause of which is an intracellular schizomycete. By discovery of a tumor-strand and of stem structure in leaf tumors (in 1911) my interest received a tremendous accession from which it had not yet recovered when the newer discoveries of this winter converted it into a white heat! I am now persuaded that the solution of the whole cancer problem lies in a study of these plant tumors. At least they must now be studied until the matter is definitely settled, pro or con.

If cancer is due to a microorganism, bacterial or other, we are not obliged *theoretically* to conceive of all such new growths as due to one and the same parasite, nor, indeed, on first thought, is such the more probable hypothesis. The first thought is that probably there must be as many parasites as there are kinds of tumors, yet certainly, on further reflection, the mere cell differences between a sarcoma, let us say, and a carcinoma do not necessarily involve the conception of two parasites. The two tumors can be explained theoretically just as well by the postulate of one parasite, and in the light of our researches on crown gall much better *by one*. If the tissue response depends on the kind of cell or cells first infected, as apparently it must, on the assumption of a parasitic origin, then, of course if connective tissue cells only are involved, we shall have sarcoma; if gland cells only are invaded we shall have carcinoma; or if both, then a tumor containing both types of cancer. Whichever cell was first invaded (the bacteria being imprisoned) would be likely to continue its proliferation as a tumor of a pure type, but other elements might eventually become infected by a surgical operation, or otherwise, *e. g.*, a sarcoma might follow a carcinoma as in some mouse tumors, and also in man, the connective tissue stroma becoming infected.

I now think the human embryonal teratomata are cancerous not only potentially, but actually from the beginning. Many of them have been recognized to be so on removal, and in the remainder the stimulating blastomous portion may have remained undiscovered owing to its relatively small size, as was the case in hairy root of the apple (and every particle of such a tumor would have to be sectioned and studied before one could deny it), or it may have receded during the rapid development of the non-blastomous purely teratoid portions. All of them, whether it be assumed that they have developed from "cell-rests" or parthenogenetically, are, I believe, due to the stimulus of a microorganism, but not necessarily of a schizomycete, since other orders of parasites may,

conceivably, give rise to the same chemical and physical stimulus.

Wilms in his book on "Die Mischgeschwülste" (Heft 3, Leipzig, 1902, p. 242), if I understand him correctly, considers the blastomous portions of embryoid tumors to be of a secondary nature, as do other writers, but in this assumption they are probably wrong.

To the statements of these authors claiming the cancerous element to be secondary, may be replied: The same could be said of the shoot-producing tumors on *Pelargonium* and on tobacco did we not know experimentally that it is actually the infected tumor tissue which is the earlier and which has stimulated the normal tissues to develop. Moreover, which tissue *is* the earlier is a matter that can not be determined by mere observation of sections (Betrachtung des Wachstums—Wilms), but one to be worked out experimentally.

To condense results, I may say that during the past winter I have discovered that when the crown-gall organism (*Bacterium tumefaciens*) is introduced into the vicinity of dormant buds on growing plants atypical teratoid tumors are produced quite regularly. I have obtained these in *Pelargonium,* tobacco (2 species), tomato, *Citrus, Ricinus,* etc. Apparently what happens is this: The bud anlage are torn into fragments by the rapidly growing tumor and these fragments are variously distributed and oriented in the tumor where under the stimulus of the parasite they grow into abortive organs variously fused and oriented, some on the surface of the tumor, others in its depths. Surface fasciation occurs. Also in the depths of the tumors fragments of organs occur, lined by membranes bearing trichomes (hairs) and lying upside down and variously oriented and combined. The flower shoots and leaf shoots on the surface of such tumors vary greatly in number and in size, often they are the merest abortions and in that case there may be a hundred or more of them (leafy shoots or flower shoots) on a single tumor, especially on the *Pelargonium.* Even the largest and best developed surface shoots if they arise out of the tumor tissue and not from its vicinity are feebly vascularized and become yellow and dry up within a few months and often before the tumor itself decays. Such shoots never come to maturity. Immature fragments of ovaries and of anthers also occur on the surface and in the depths of such tumors.

These teratomas when produced in leaf axils on the castor oil plant reach a large size and perish quickly, *i. e.,* often within 2 months. Frequently in this plant the neighboring glands on the base of the leaf stalk are also invaded (within 2 or 3 weeks) and greatly enlarged. This is one of the striking results on *Ricinus* to which I would call special attention, since it is very suggestive of what often occurs in cancer in man, that is, of the malignant enlargement of lymph glands in the vicinity of a cancer. Following inoculations on the middle part of the leaf-blade of *Ricinus* I have also traced a parenchymatic tumor-strand down the petiole a distance of 11 cm. This was nearly circular in cross-section, large enough to be visible to the naked eye and composed of parenchyma cells. Corresponding to this were swellings on the surface of the petiole and bulging into the petiole cavity, but no ruptured tumors. No teratoids were formed on the *Ricinus* leaves.

Daughter tumors are produced freely on tobacco if the inoculations are made early enough, and these often reproduce all the teratoid elements of the primary tumor, *e. g.,* daughter tumors 10 inches away from the primary tumor may bear leafy shoots. These secondary tumors, which have been seen both in stems and in leaves, are con-

nected with the primary tumor by a tumor-strand which is lodged in the outer cortex and is vascular, *i. e.*, has the structure of a diminutive stem (stele).

What is still more astonishing, I find that I can produce these teratomas in the leaves of tobacco plants, where no dormant buds are known to exist.[8] To get these results the leaves must be fairly young, *i. e.*, plastic. They will then produce tumors where they are inoculated (needle-pricked) and many of these tumors will be covered with leafy shoots (tobacco plants in miniature). I have obtained seven such teratomas from the blade of a single leaf, and twenty-seven from the leaves of a single plant—too many to be due to Cohnheim's "cell-rests." They must have originated, I think, from groups of plastic (totipotent) cells normal to the inoculated parts of the leaves and probably also present in many uninoculated parts of such leaves, if not in all parts.

How, then, can these phenomena be explained? The teratoids I have obtained being essentially like the embryonal teratomas in animals, I believe that in both plants and animals they must have the same origin, *i. e.*, must arise from an identical chemical and physical stimulus. So far I have been able to explain the embryonal teratomas only on the assumption that in all animals and in all plants (except the simplest) certain widely distributed normally arranged cells or groups of cells, possibly all cells when very young and plastic carry the potentiality of the whole organism, which potentiality is not ordinarily developed on account of division of labor, but which comes into action when hindrances are removed, *i. e.*, when the physiological control is disturbed or destroyed. We know that life must have begun so in unicellular plants and animals and there is no good reason why it should not have continued so in multicellular ones. Only we have not been accustomed to think of it in this way, yet there are many facts respecting regeneration of lost parts in both plants and animals which coincide perfectly with this view. Coinciding with this view as to the origin of embryomas in various organs, *i. e.*, from groups of normal but very young undifferentiated or but slightly differentiated cells or groups of cells multiplying under a cancer stimulus, is the fact that I have been able to produce the teratomas in tobacco leaves only by inoculating very young leaves. When older leaves are inoculated they either do not respond or yield only the ordinary crown galls.

I may be permitted a few general remarks in conclusion, premising that this is the way the cancer problem looks to an experimental biologist.

With some praiseworthy exceptions, the cancer specialists of to-day, following the lead of the Germans, and their English imitators, are lost in a swamp of morphology, and it is time that an entirely new set of ideas should be promulgated to rescue them from their self-confessed hopelessness.

When a pathologist can say: "Concerning the ultimate nature of neoplastic overgrowth we shall never have more than a descriptive knowledge," he has reached the end of the road in his direction and the limit of pessimism! I do not care a rap whether I am called orthodox or heterodox, but I do care tremendously to keep an open mind and a hopeful spirit. One trouble with too many cancer specialists is that they are not *biologists*, whereas the cancer problem is peculiarly and preeminently a biological problem. These cancer morphologists have patiently cut and stained and studied hundreds of thousands of sections of tumors, fining and refining their defini-

[8] See *Journal of Agric. Research*, April 24, 1916, Plate XXIII.

tions and distinctions and *building up high walls of separation where nature has made none*, all because they do not understand the plasticity of living, growing things. I do not mean to condemn the study of sections, but only to suggest that there are also other ways of looking at this problem, which is one of growing things. There is too much reasoning in a circle on the part of many of these writers, too much argument basing one assumption on another assumption as if the latter were a well-established and solid fact, too little clear thinking of a biological sort, too little first-hand knowledge of living plants and animals, too much dogmatism, too much *orthodoxy*, and not enough experimentation. Hence the pessimism and the discouragement.

Cancer research was born in Germany and has been prosecuted there more diligently than anywhere else in the world, and they have done wonders in the study of its morphology, but etiologically the best the Germans have been able to do has been to cover the whole situation with a cloud of obscurity. With a few uninfluential exceptions they have denied the parasitic nature of the disease and discouraged search for an organism, and in this pessimistic attitude they have been ably seconded by their English followers. These strong men, chiefly morphologists, have dominated the situation for a generation, but they have not explained cancer and they can not explain it, and they must now give way. Indeed, from Cohnheim to Ribbert there is not one of their arguments in opposition to the parasitic nature of cancer which is not as full of holes as a skimmer!

Listen to Ribbert in his last great book:[9]

Denn wenn auch durch Mikroorganismen knotige, tumorähnliche Wucherungen hervorgerufen werden können, so handelte es sich doch stets nur um die Bildung eines entzündlichen Granulationsgewebes, das höchstens mit Tumoren der Bindegewebsgruppe eine gewisse Ähnlichkeit haben konnte (p. 378).

In other words, the most that parasites can do is to produce a granulomatous tumor superficially like a sarcoma.

Again he says:

Aber wenn das fremde Lebewesen die Zellen bewohnt, müssen diese notwendig geschädigt werden. Das folgt aus dem Begriff der Parasiten, der selbstverständlich der Zelle nur Nachteil bringen kann. Damit ist aber die den Tumor characterisierende Steigerung der Wachstumsfähigkeit der Zelle nicht vereinbar (p. 384).

In other words, when a parasite occupies a cell that cell must necessarily be injured. It follows out the very concept of a parasite that it can only bring injury to a cell, and the characteristic increase of cell growth in tumors is incompatible with this idea. Here as usual he just misses the point.

Ribbert ends his great book, of which "seine Entstehung" is its weakest part, although the illustrations are also to be criticized because they are all vague wash drawings when they should have been exact photomicrographs, as follows:

Das Karzinom entsteht auf Grund einer durch Epithelprodukte bewirkten die Differenzierung des Epithels vermindernden und sein Tiefenwachstum auslösunden subepithelialen Entzündung.

In other words, if I understand him, cancer is due to a subepithelial inflammation induced by substances arising in the epithelium, which substances cause it (or which inflammation causes it) to be less well differentiated and to grow downward. This, etiologically, is about as clear as mud!

Wilms, also, at the end of his book,[10] sarcastically inquires:

Welches Bakterium soll wohl eine Keimblattzelle, Mesoderm- oder Mesenchymzelle producieren können, die dann embryonale Gewebe und Organanlagen bildet?

[9] "Das Karzinom des Menschen sein Bau, sein Wachstum, seine Entstehung," Fr. Cohen, Bonn, 1911.

[10] "Die Mischgeschwülste," p. 275.

To which may be replied *Bacterium tumefaciens,* and probably others!

This is his additional and closing sentence designed to be a finality of invincible logic:

Wer diese genannten angeborenen Sarkomaformen als durch Bakterien erzeugt betrachtet, übernimmt damit die Verpflichtung, auch für die Bildung seiner eigenen normalen Gewebe und Organe eine bakterielle Infektion nachzuweisen.

To which may be answered: Very well, and why not? Since a bacterial organism does just that in the plant!

I believe these old ideas and assumptions must be sifted, turned and overturned, and many of them wholly rejected if we are to find the truth.

Cancer, according to my notion, is a problem for the experimental biologist and the bacteriologist. The morphologist has gone as far as he can go and the energy of cancer research from now on must, I believe, be turned into new channels, if we are to expect results commensurate with the needs of humanity.

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ESTABLISHMENT OF A SCHOOL OF HYGIENE AND PUBLIC HEALTH BY THE ROCKEFELLER FOUNDATION

IN recognition of the urgent need in this country of improved opportunities for training in preventive medicine and public-health work and after careful study of the situation the Rockefeller Foundation has decided to establish a school of hygiene and public health in Baltimore in connection with the Johns Hopkins University, where it is believed that the close association with the Johns Hopkins Medical School and Hospital and with the school of engineering of the university furnish especially favorable conditions for the location of such a school. Dr. William H. Welch, now professor of pathology, and Dr. William H. Howell, professor of physiology in the university, will undertake the organization of the new school in its inception. The trustees of Johns Hopkins University have appointed Dr. Welch as director of the school, and Dr. Howell as head of the physiological department.

Funds will be provided by the foundation for the purchase of a site and the erection of a suitable building, in proximity to the hospital and the medical laboratories, to serve as the institute of hygiene, which will be the central feature of the school. Here will be housed various laboratories and departments needed in such a school, such as those of sanitary chemistry, of physiology as applied to hygiene, of bacteriology and protozoology, of epidemiology and industrial hygiene, of vital statistics, a museum, library, etc. Additional facilities for instruction and research will be supplied by the medical and engineering schools, the hospital and other departments of the university. Funds will be provided by the foundation for the maintenance of the school in accordance with plans which have been submitted.

It is expected that the school will be opened in October, 1917, as it is estimated that a year will be required for the construction and equipment of the institute and the gathering together of the staff of teachers.

As it is recognized that the profession of the sanitarian and worker in preventive medicine, however closely connected, is not identical with that of the practitioner of medicine and requires a specialized training, the school of hygiene and public health, while working in cooperation with the medical school, will have an independent existence under the university, coordinate with the medical school.

The school is designed to furnish educational and scientific opportunities of a high order for the cultivation of the various sciences which find application in hygiene, sanitation and preventive medicine, and for the training of medical students, physicians, engineers, chemists, biologists and others properly prepared, who wish to be grounded in the principles of these subjects, and above all for