APPOSITIONAL GROWTH IN CROWN-GALL TUMORS
AND IN CANCERS

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Fifteen years ago some sections were cut for me from a tumor which I had produced in the cortex of a young tobacco plant by means of a single needle-prick introducing the Paris daisy strain of Bacterium tumefaciens Sm. and T. This was a young tumor, that is, one only three weeks old, and the sections were cut and stained in series. In the rush of other work these sections were overlooked and as they had been stained with a fugitive stain they faded so that when I came to examine them some years later there was a shoal of pale tissue surrounding the tumor which I could not in the least interpret. The cover-slips were removed by soaking in xylol and the sections restained, whereupon I was face to face with a new phenomenon (new to me). I had before me what cancer specialists have called conversion of normal cells into tumor-cells by apposition, that is by contact of the diseased with the normal, the "shoal" proving to be a 0.5 mm. wide layer of cells intermediate in character between the normal cortex-cells and the tumor-cells. By intermediate I mean midway in size and affinity for tumor-stains, and showing various transition stages including here and there a surrounded unchanged cortex-cell. (See this Journal, vol. i, 1916, no. 2, fig. 78).

I was much impressed by the phenomenon and in searching through other boxes of sections I found evidence of it in various tumors due to Bacterium tumefaciens including some produced in the cortex of the Paris daisy. The phenomenon is also shown

1 An abstract of this paper with lantern slides was presented May 1, 1922, at the meeting of the American Association for Cancer Research in Washington.
on plate 29 of Bulletin 213 (l.c.), published in 1911, but the evidence in this figure had not then specially attracted my attention and is not mentioned in the text. That there is here conversion of normal cells by apposition rather than invasion of normal tissue by cells growing out of the originally infected cells, or than simply an irritation-response of the host-cells which never passes over into tumor-tissue, there can be no question whatever for the cells have not changed places but the change has occurred in situ by the conversion of large cells wholly normal into congeries of small cells having all the characteristics of tumor-cells and visibly surrounded in many cases by the stretched wall of the original cell. An irritation-response that does not pass over into tumor tissue proper also occurs in the vicinity of many crown galls, viz., an overgrowth of wood and bark, due to the stimulus of an extra amount of food moving in the direction of the tumor in greater quantity than it can use, so that some part of this excess either never actually reaches the tumor or oozes backward from it into the adjacent tissues, which are thereby incited to excessive growth; but this is something quite different from the response we are here dealing with because the cells of the hyperplasia in the one case have normal arrangement, normal staining properties, and function more or less normally whereas the cells in the other (the appositional growth) are smaller more or less disoriented and stain and behave like tumor-cells. For figures showing thickening of the wood entirely outside of the tumor but influenced by it see Bulletin 255 (l.c.), plates 25, 62A and 63, or An introduction to bacterial diseases of plants, fig. 319, subs 5 and 6. These proofs should convince any one that the phenomena here described are not the same although both kinds of growth are brought about by the presence of the tumor.

In 1916 I tried to reproduce the phenomenon of growth by apposition in tobacco-tumors, using the hop-strain of the crown-gall organism and single needle-pricks as before, but the gall was growing very slowly when collected and I got nothing com-

\* See also my paper in Phytopathology, 1922, xii, pp. 265-269, pl. xviii.
parable to the earlier results which were produced, it will be remembered, with another strain of the organism.

In 1920 I repeated the experiment once more using, as in the first instance, the Paris-daisy strain for the inoculations. These inoculations were on the stem (cortex) of two young, growing tobacco plants by means of single needle-pricks in the manner shown on plate 1A. The aim in all cases was to confine the punctures to the cortex, making them as shallow as possible. In some instances it is likely that the outer phloem may have been reached but not the wood or pith and yet the wood is split open by the growth of the tumor-tissue and the pith is invaded. The tumors were collected and fixed in Carnoy's fluid (one-quarter glacial acetic acid, three-quarters absolute alcohol) at the end of three weeks. Sections in series have now been cut and stained from 15 of these tumors, and every one shows on some part of its periphery the same phenomena observed in the tumor of 1907. All the tumors when collected were increasing in size and in many cases this increase had been so rapid that remoter tissues were crushed. This expansion was partly from continued division of deep tumor-cells (as shown by an occasional mitosis) but also and chiefly from peripheral growth, i.e., by conversion of neighboring normal cortex-cells (young cells, be it remembered) into tumor-cells, as shown in tangential section and in cross-section on plates 6, 7, 8, 9, 10. See especially plates 3B and 4, where the crushing is confined to the tissue bordering those lobes of the tumor which show marked appositional growth. This particular localization of the crushing, indicating excessive pressure, has been observed also in other tumors of this series (plates 2B, 10, 23).

Not in one only but in all of these galls there is the plainest evidence of tumor-growth by *apposition*, that is, peripheral extension of the tumor further and further into the cortex by the conversion of the adjacent normal cortex-cells into tumor-cells. One cortex-cell may give rise to a hundred or more tumor-cells. The sections show only a narrow periphery of cortex-cells undergoing conversion into tumor-cells (generally only a thickness of 0.5 mm. or less) but with the conversion of these
cells a new and remoter series of cells is subjected to the influence of the tumor with the same result, provided of course there has been no crushing, the tumor increasing in size as long as conditions for its growth are favorable.

Beyond the tissue in process of active conversion is a variable width of cortex-cells which are larger than the normal cortex cells, often twice their diameter but otherwise apparently nearly normal. For evidence of this plates 1B and 5 may be compared with plate 1A. This may also be seen clearly in 2A, 2B and 3A, and more highly magnified and very strikingly on plate 8. These cells have large nuclei and are dividing more freely than the normal tissue but not nearly as rapidly as the active transition tissue, and they are not different from normal cells in their orientation, in their intercellular aeration or in their relation to stains. These enlarged cells of the cortex are perhaps only cells stretched by proximity to the growing tumor, or enlarged and dividing on account of a more abundant water-supply, and yet we cannot say that they are not under a more direct influence of the bacteria which are the cause of the tumor. They are indicative at least of the nearby presence of tumor-tissue, quite as much as are the elongated glands surrounding a stomach carcinoma. The cortex in this region (round about the tumor) is often twice as thick as the normal cortex without having any more or at least many more cells in its structure. This may be seen very clearly from plates 2 and 3, prepared from 3 tumors where the enlarged cells form a sort of cushion on which the tumor rests.

I am the more inclined to publish my observations on appositional growth in these plant-tumors because of very positive statements by many cancer specialists, from Waldeyer, Cohnheim and Virchow down to Hauser, Krompecher, v. Hansemann, Petersen, Cornil, Fabre-Domergue, Menetrier, and others, as to the occurrence of appositional growth in carcinoma, and because in many respects crown galls are better adapted to the study of this phenomenon of growth by apposition than animal tumors, not only because we know them to be due to an intracellular schizomycete so that there is a definite reason for such growth, but because they can be reproduced at will and collected for
examination at any period of growth, and finally, because there are no migratory cells to confuse the picture.

Under dominance of a theory which has required them to ignore or explain away the plainest phenomena looking toward parasitism, Ribbert and his followers have denied the occurrence of growth by apposition in cancer. Cohnheim’s theory of cancerous growth from misplaced embryonal tissue (cell-rests) having been abandoned, Ribbert’s “nipping-off” theory was substituted, that is, growth of cancers wholly out of themselves, beginning in a fragment of epithelium dislodged by inflammatory connective tissue disturbances, or by trauma, and buried in the deeper tissues where it acts as an irritant and where it becomes converted into malignant tissue, but with the *How* or *Why* of its conversion remaining always unexplained. Ribbert at first maintained the origin of cancer from a single cell or cell-group and explained the appearance of islands of malignant tissue around the parent-tumor as due to deep strands of tumor-cells from the parent-tumor which, turning outward and upward, formed contacts with the epithelium immediately around the parent-tumor and thus gave the deceptive appearance of independent small growths. But Ribbert’s theory also being now in less favor than formerly because frequently contrary to observed phenomena (Krompecher’s, Petersen’s, Adami’s (1), and Cullen’s, for example) there is once more the possibility of interpreting the undenied phenomena in consonance with what I shall here demonstrate to be true of crown gall, an indisputable bacterial tumor with various resemblances to malignant animal tumors.  

Because of the importance of the subject I shall cite

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Crown gall of plants. Erwin F. Smith. Phytopathology, 1911, i, 7-11, with 2 plates.


some of the views of leading oncologists pro and con, premising that the whole subject from the human and animal side should be worked over again using only primary tumors, acting on tissue of the same type, and preferably young tumors arising in columnar epithelium.

Ribbert's view, as set forth in chapter V of his last work Das Karzinom des Menschen (2) is as follows:

From the microscopic behavior of cancer it cannot be doubtful that the parts invaded are for the most part destroyed. Where the cancer has fully developed, we cannot demonstrate the previously existing tissue. But the naked eye might be deceived. For the thought is near, from the microscopic appearance, that the bordering parts may have been converted into the carcinoma and in this way have disappeared where the tumor is found.


Cancer in plants. Erwin F. Smith. Proceedings of the Seventeenth International Congress of Medicine, held in London, August, 1913, III, 18 pp. Also a separate.


Undersøgelser vedrørende nogle svulstlignende Dannelser hos Planter. [Investigations concerning some tumor-resembling growths in plants.] C. O. Jensen Kgl. Veterinaer-og Landbohøjskoles Aarsskrift. Serum Laboratory no. liv. Copenhagen, 1918, 1 colored plate, and 17 figures in text.


This was the assumption formerly for many tissues. It was believed to have been demonstrated by histological investigations that other cells reached by the carcinoma were converted under its influence into cancer cells, that these consequently had an essential part in the spread of the tumor. *This view, if it could have been accepted as true, would have been of great importance.* Because from it would follow, that to the growing cancer *infectious characters* must be ascribed either dependent on the presence in the cancer of a parasite, or resting on specific chemical products produced by the tumor (p. 191).

It is remarkable that this view should have been maintained so long. One could understand it, if it related only to the acceptance of the view that cancer stimulates the bordering cells into growth. . . . . But that one should think the cells of the carcinoma brought those of the other tissues not only to multiplication but also made out of them genuine carcinoma cells, this shoots wide over the mark (p. 191). . . . .

Men assumed and still assume that epithelium of like origin can take part in the growth of the tumor, that it is drawn into a cancerous proliferation and so the carcinoma grows. To this view I have been opposed for almost two decenniums. *It is unquestionably false.* But in spite of all my efforts and those of Borrmann who has ably supported me, it is not yet completely overthrown (p. 215). . . . .

Really, for the explanation of the growth of cancer in general this erroneous view could very well be discarded. For even if here and there an appositional growth actually occurs, it can have only a negligible effect upon the spread of the tumor. . . . .

This is, therefore, not the ground which has led to the maintenance of the old doctrine. Decisive rather have been views on the origin of carcinoma (p. 215).

Ribbert speaks of the fact that the beginnings of carcinoma cannot be found often enough for study, and in their place men have hoped on the borders of a carcinoma in the same type of epithelium to find and study equally well its beginning stages.

My doctrine that cancer grows only out of itself was naturally disagreeable to views of this sort *und man bemühte sich mich zu widerlegen* (p. 215). . . . .

Perhaps one would not have taken the great trouble to seek out those cellular conversions, if he had had a clear conception that with *Doctrine not original with Ribbert but borrowed from the Frenchman, Bard.*
the discovery of cancer-like cells newly arisen out of the neighboring epithelium, the difficulties of explaining the genesis of carcinoma would be only so much the more increased.

How then should the cell metamorphosis take place? The one meaning could be this, that from the cancer infectious influences proceed to the neighboring cells, through which these cells are biologically changed. But this view could be maintained only so long as one still thought the cancer a parasitic disease—and even here without any foundation because parasites never change cells but only injure them. [The italics are mine, and the plates I show are a sufficient refutation of this statement.] But today, when we have universally given up the infectious theory of cancer there can be no more talk of any such explanation (p. 216).

Aber es ist ja gerade das wichtigste Ergebnis aller meiner bisherigen Untersuchungen und meiner Darstellung im Abschnitt V dieses Buches, dass die Anschauung, der Krebs wüchse durch stets erneute Apposition sich Krebsig unumwandelnder Epithelien, falsch ist. Der völlig entwickelte Krebs wächst immer nur aus sich heraus (p. 482).

Ribbert maintains that no outside influence, parasites for example, or any symbiosis, can possibly induce cell-proliferation:

Es ist aber natürlich ein Fehler, das, was man bei der Symbiose sonst nicht beobachtet, auf das Gebiet des Krebses willkürlich zu übertragen.

Von den meisten Seiten wird denn auch die Symbiose nicht zur Erklärung herangezogen.


5 On the contrary from an etiological standpoint they are tremendously simplified and the phenomena are brought into correlation with what occurs in the plant.
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welche Hindernisse, Hemmungen, Spannungen fort und dann wächst die Zelle (385–386). . . .

Wie wir also die angenommenen Parasiten auch wirken lassen wollen, ob durch Aufhebung der intrazellularen Spannung oder durch ‘karzinomatöse Umwandlung’ (‘Degeneration’!) oder durch Symbiose, in keinem Falle leisten sie uns irgend etwas für das Verständnis der Krebsgenese (pp. 386–387).

To all of this we may reply in Ribbert’s own words:

Was nützen uns alle Spekulationen? Ohne Tatsachen kommen wir nicht weiter (p. 461).

The best defense of Ribbert’s theory is by Borst in Die Lehre von den Geschwülsten (3), and from this I cite at some length making my own translation as in the other cases.

Then the further growth of the tumor takes place not by continual conversion (Einbeziehung) of the normal surrounding tissue into the same sort of degenerative growth, but the tumor develops out of itself. . . . . If I speak here positively it is because I have given special attention to this point in my own extensive studies. Even now, most specialists hold to the doctrine of a peripheral growth in carcinoma [the italics are mine] in the sense that continually, close around the tumor, cells of ordinary and of glandular epithelium, hitherto normal, undergo a cancerous change (Hauser, Beneke, and others). Formerly this view of the growth of carcinoma (and of tumors in general) was the universal one. It was conceived that an agent of unknown nature inciting to proliferation was distributed in the periphery of the carcinoma and that this agent changed the hitherto normal cells into a cancerous growth; sometimes this agent was pictured as a fluid menstruum, sometimes as a mass composed of the finest granules (Gussenbauer), sometimes the cancer cells themselves were supposed to contain a substance which could exercise this growth-irritation on the surrounding cells. Subsequently, making use of the data of bacteriological and parasitological investigations, parasites were thought of as possible causes. Beneke speaks in a general way of an ‘Umstimmung’ of the normal cells, of a reciprocal influence of the cells which makes possible a transfer of the ‘Blastomatosis’ from cancer cells to physiological cells.

The opinion that in cancer progressive growth takes place in this way, that the bordering parts are continuously drawn into the degener-
erate growth ('Nachbarinfektion') was based chiefly on histological transition appearances (Borst, Bd. II, 697–698).

Borst does not deny the existence of such appearances in the vicinity of cancers but he denies that they are transition stages. He thinks he has another "simple and plausible explanation." He says the same changes occur in inflammatory conditions and in regenerative new formations, especially in regenerative processes complicated and disturbed by inflammatory processes.

Under these conditions very striking atypical epithelial growths arise, which Friedländer, more especially, has fully described, and which have absolutely nothing to do with cancerous degeneration. . . . . In the course of chronic inflammations the regeneration of common epithelium and glandular epithelium often gives pictures strikingly like cancer (Borst, II, 698–699).

But along with disputed doubtful spots on the edge of a carcinoma we find other spots in which plainly beyond any doubt entirely unchanged, normal epithelium lies close up against carcinoma parenchyma without a trace of progressive change to be observed in the former, on the contrary often enough disintegrating (rückläufige) metamorphoses are to be found. The proliferative processes in the common and glandular epithelium just beyond the periphery of carcinomas are therefore of the same order as the multiplication of the connective tissue, of the blood vessels, of the bony tissue, etc., which we have learned to regard as reactions of the connective substance against the penetrating carcinoma. Hence the fact, that in the tissues roundabout a carcinoma through the secondary occurrence and fusing of parenchyma masses of the carcinoma with neighboring, preexisting epithelial masses which are normal or in process of a growth reaction, pictures arise which might be interpreted as a transition of normal epithelium into cancerous, and many times have been so interpreted, as we have already mentioned. The following point is also important: many carcinomas more or less completely resemble the mother-tissue, and often to such a degree that we can find all sorts of transitions from very crude (stump­erhaften) imitations to the formation of almost typical forms in one and the same tumor; if we add that these forms recalling the mother­tissue (e.g., glandular tubes) also recall or may recall by their grouped arrangement and fusion, the coarser structure of the mother­tissue (e.g., glandular lobes that occur in cancer of the breast) it is easy to
see how the deception would arise that one has before him nothing less than normal structures (e.g., gland-lobules) in process of cancerous conversion. The absence of excretory ducts in such groups of cancer bodies, the lack of a membrana propria, the betraying irregularity in the formation of the cancer-body in spite of all other resemblances, its extraordinary multiplication, and so forth, will serve to prevent confusion. In consideration of all these circumstances and especially with the use of the finer histological technic which shows us clearly the difference in nuclear and protoplasmic structure and in the type of mitosis, we shall not in most cases be deceived into believing that on the periphery of a carcinoma we have a transition from normal epithelium into a carcinomatous parenchyma (Borst, II, 699–700).

Borst says it has been established that endothelial cells are not converted into cancer-cells and that when a cancer in one sort of epithelium impinges on another sort of epithelium there is no conversion of the latter. But this his opponents except Carl Gussenbauer (4) also admit.

With the above limitations the importance of the growth of carcinoma by a peripheral change of normal parts is greatly reduced; it is therefore certain that by far the greater part of every carcinoma grows out of itself, and that only where the carcinoma abuts on cells of like origin may a cancerous conversion of normal tissue take place. But also against this last cardinal point of the theory of 'tissue infection' in cancer all the above mentioned considerations are opposed (Borst, II, 701–702).

Borst's book is very attractive and he seems to be a fair debater since he cites his opponents and does not distort their views. I think, however, he is swayed a good deal by his preconceived ideas as to the cause of cancer. If he thought it due to a parasite, then he would interpret the admitted facts in quite another way. Most of his above mentioned sources of error are such as would apply to the interpretations of tyros rather than to those of experts of a like experience and reputation with himself.

6 Here we may distinguish clearly, as Borst does not, between clinical importance and etiological importance.
For older views concerning growth of tumors by apposition I should like to cite Virchow and for more recent views Hansemann, Hauser, Krompecher, Petersen, Menetrier and others.

Virchow (5) writes as follows:

Earlier than the stage of the formation of the formative cells or primordial cells [of the tumor], as they have also been called, a whole series of changes have taken place, and the tumor does not begin where the formative cells lie, but there where the first change in the mother tissue took place [or, to use a modern phrase, in the precancerous stage].

From this we see that a true boundary between the tumor and the mother tissue is not present; at the beginning the tumor is in complete and intimate connection with the mother tissue (Vol. i, p. 93).

Hansemann in 1897 (7) writes as follows:

It is in general plain even from a macroscopic observation that the primary tumors end diffusely in the surrounding tissue, while the secondary tumors are sharply delimited from the organ-parenchyma (p. 124).

Hansemann speaks of a collateral hyperplasia in the vicinity of primary tumors. This is a common occurrence, as every one knows who has studied cancer. He says:

If we begin first with the primary tumors, we shall see that in the vicinity of such a tumor, the tissue out of which the tumor has developed, and also the related tissue, becomes hypertrophied with great regularity, although there are some exceptions. In the vicinity of a cancer of the skin (canceroid), of the mucous membrane and of the oesophagus the epithelial margins are widened and elongated, and the papillary bodies are enlarged. The sweat glands and sebaceous glands may also be involved and this general hypertrophy gradually extends outward. All the layers of the skin are involved in this hypertrophy, the germinal layer, the rete, and also the cutaneous layer in case of epidermoidal formations. Also the mucous membranes with ciliated epithelium and cylinder epithelium become thickened or more often

1 For many interesting figures of edges and early stages of cancers showing this see Thos. S. Cullen: Cancer of the uterus.
become epidermoidal in the vicinity of a primary carcinoma, the latter especially if they have become cancroid through cell-variation [by cancroid he means a keratinizing cancer]. In stomach and intestinal cancers we see the gland-tubules in their vicinity elongated and also in cancer of the uterus and eroding carcinoma of the portio there is a growth of the glands in the vicinity into long tubules. These collateral growths are often of such dimensions that they constitute special tumors. On the outer skin, and especially in the larynx, verrucose thickenings and great warts arise, which might be taken for benign growths if they alone were excised for the examination. In the intestinal tract, in the uterus and in the bladder, papillary cauliflower-like excrescences arise which may also lead to confusion (pp. 125–126).

But where the collateral hyperplasia arises, it passes over so gradually into cancerously changed tissue, that often under the microscope we cannot tell exactly the cells which mark the boundary between the two conditions. Ribbert (pp. 143–150) has called attention to the interesting fact that carcinoma of the skin and mucous membranes, of the breast, etc., proceeding from a center may grow outward and fuse with the epithelium of the mother-organ, so that it may appear in close union with the latter. For this reason the carcinoma [at the point of fusion] may seem to have begun independently, whereas really it is only a secondary growth. I can fully confirm this observation of Ribbert, but I am not of his opinion that we may generalize this fact so as to apply it to all cases. Indeed, I believe that Ribbert’s account applies only to a minority of the carcinomas, while in the greater number of cases an actual conversion of hyperplastic tissue into tumor-parenchyma occurs. Upon this collateral hyperplasia depends the observation that primary tumors both to macroscopic and often also to microscopic observation end rather diffusely in the surrounding tissues. In this they are quite distinct from the metastases, because the latter usually have sharp boundaries (pp. 126–127).

Rokitansky taught that the center is the youngest part of a tumor but Virchow (8) showed that the periphery is the youngest part (it is also the youngest part of a crown gall) and taught that one must study the margins of tumors if one would learn how they develop. Concerning this Hansemann remarks:

Up to this time all writers on cancer have followed this dictum and they were the more inclined to do so because everyone believed that a
primary tumor grew in this manner, that out of its vicinity an ever increasing number of parts were converted into the tumor mass. On the contrary quite recently Ribbert (Hugo Ribbert: Pathologische Wachstum der Gewebe, Bonn, 1896) has offered objections. . . . . It must be recognized that there are such appearances as Ribbert describes and that he is correct in maintaining, for his cases, that the carcinoma proceeds from the surface and then from the depths again grows back to the surface, in order to appear here in union with the normal elements of the parenchyma. . . . . Ribbert's mistake lies in having generalized his conclusions and in declaring that there is no other method of propagation. Indeed, I maintain that this other way is the principal way. I possess a whole series of preparations of epidermal carcinomas, of stomach and intestinal cancers, etc., in which I can demonstrate it indisputably, and in which any fusion in Ribbert's sense is out of the question (pp. 156-157, 1st ed., and 199-200, 2d ed. 1902).

Hansemann sums up as follows:

We must, therefore, I believe, maintain that malignant tumors arise from a restricted spot, even from a single cell, and these enlarge out of themselves, but that also they may arise contemporaneously or successaneously over large areas and besides their growth out of themselves, which naturally always occurs, may grow by confluence and by apposition (p. 157).

Nobody yet has seen to a certainty the very earliest stages of carcinoma, even Ribbert, who claims his tumors alone as sufficiently small and all others as too far advanced, to decide the question. Nevertheless, it is only possible to recognize a thing as carcinoma if it has plainly the structure of the latter; then, however, it is a definite structure and not a becoming. So long as it is still in process of originating, we cannot know what it will become when it has grown farther (p. 158).

No man has ever seen a tumor arise under the microscope (p. 154).

In 1910 von Hansemann (9) also wrote as follows:

Von grosser Bedeutung sind die Beziehungen der bösartigen Geschwülste zur Nachbarschaft. Wenn eine Geschwulst wächst, so kann sie auf die Nachbarschaft in verschiedener Weise einwirken, entweder verdrängend oder auflösend, oder wucherungserregend. . . . (p. 14)

Besonders bemerkenswert ist der Umstand dass Karzinome, die von
In opposition to Ribbert, Hauser (10) also found in cancer of the stomach and large intestine, in about 80 per cent of his cases, no metastases of the epithelium when there was peripheral conversion of the glands into cancer (p. 492). He says:

On the other hand as I have shown [pages and plates cited], in these same stomach and intestinal cancers primary changes of the gland epithelium occur which are unquestionably specific for carcinoma, since they are observed nowhere else, so that out of these changes alone cancer can be diagnosed (p. 492).

The same thing occurs, he says, in cylinder epithelial cancer of the uterus (492).8

Hauser's paper is accompanied by one plate containing two figures, both of which are tremendously interesting, especially his figure 2 which shows, enlarged, the transitional border line of an intestinal cancer, i.e., conversion from cylinder-cell normal gland tissue to a kind of irregular squamous-cell cancerous tissue. Here the epithelial cylinder cells in the outer part of a gland-tubule are normal, the middle cells of this tubule show transition forms, while the inner half of the tubule is wholly cancerous, has fused with the cancerous cells of an adjacent tubule and has broken through the muscularis mucosae, as is clear from his figure 1, which gives the orientation of his figure 2 (fig. 1 of my copy).

Excluding many cases of carcinoma solidum and gelatinosum, we find these specific cancerous changes of the glands of the mucous membrane especially in that form of carcinoma cylindro-epithel adeno-matosum, in which in consequence of active multiplication the one-layered epithelium becomes several-layered while at the same time the epithelial cells themselves experience profound morphological changes. They lose completely their cylindrical form, become exquisitely polymorphous, resembling the cells of the many-layered pavement epi-

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8 In this connection see Cullen (I.e.) figs. 138, 196, 198, 209, 214, 230, 233, 234, 235.
thelium, the nucleus becomes larger and often extremely chromatin rich, the protoplasm appears fine granular, the normal mucin (Schleim) has everywhere ceased, so that even in the large intestine there is not anywhere any more production of beaker cells, and the whole epithelial layer shows an intensive staining. . . .

All these profound changes of the glandular epithelium, or of the glands of the mucous membrane, which we have to consider as a specific cancerous conversion (Entartung) of the glands of the mucosa, because it occurs exclusively in carcinoma, we may observe in suitable objects with fully preserved membrana propria, and at a time when the cancerously degenerated gland-tubules have not yet anywhere broken through the muscularis nucosae . . . . (p. 493).

Finally, as to the question whether it is possible that a carcinoma may arise through the metastasis of normal epithelium alone, that is, without change in its biological characters, such a possibility according to my notion is wholly excluded. . . . It is in opposition to the normal laws of growth.

The cancerous development can rest therefore only on a fundamental change in the biological peculiarities of the epithelial cells. Only such an hypothesis can explain the fact that normal body-cells in their later generations acquire definite parasitic peculiarities (pp. 496–497).

For the specific cancerous conversion of epithelium, at least in cylinder-epithelium carcinoma, we have a definite morphological standpoint: The loss of physiological function, the change of typical cylinder
epithelium into several layered polymorphic epithelium, the changed size-relations, especially the very frequently observed enlargement of the cells with enlargement of the nucleus at the same time and increase in the chromatin contents, further the changed form of the mitoses, the very abundant appearance of hypochromatic, hyperchromatic, asymmetrical and multipolar cell-division figures and finally the enormous capacity of the cancer cells for multiplication which is clearly connected with a certain feebleness and shorter life—all these changes, very pronounced in many cases, in my opinion point clearly to the fact that the cancer cell has become another cell, morphologically and biologically, from the mother cell from which it has descended, that an Entdifferencirung or Anaplasia, as Hansemann calls it, in short a 'specific cancerous degeneration' has taken place (pp. 497-498).

As to the impulse causing this cancerous degeneration of the epithelium, we know nothing (p. 498).

Hauser also refers repeatedly to growth by apposition in his book on cancer of the stomach and intestine (11). Here he says:

For the further growth of the primary cancer proceeds generally in this manner, that while on the one hand the epithelial growth which has broken through into the submucosa pushes outwards in all directions and penetrates ever deeper into the tissue, on the other hand the cancerous degeneration of the glands of the mucous membrane on the periphery of the cancerous mass progresses continually, so that, over and over, new glands, cancerously degenerated, break through into the submucosa. . . . . This centrifugal growth of the cancerous new formation brought about by apposition, is in many cases of carcinoma of the stomach and intestines, especially in the simple and scirrhous forms, the preponderating one. . . . .

The cancerous degeneration of the glands of the mucous membrane, continually progressing on the periphery of the primary tumor, appears in most cases to persist uninterruptedly to the end of the cancerous disease, that is to the death of the individual. For otherwise it is inexplicable that on the periphery of the carcinoma, whether the latter be large or small, ulcerated or not, almost without exception we find glands which show the most varied stages of cancerous degeneration even to penetration of the deeper layers of tissue. In many cases, this progressive disease of the glands appears to be quite uniform in all
parts of the periphery so that under microscopic investigation of numerous and suitable spots of the carcinoma’s edge everywhere the same behavior is to be observed. But also we frequently find a more or less great irregularity in the progress of the cancerous gland degeneration in that while the same proceeds vigorously in some parts of the cancer it appears to have ceased in other parts, either wholly or partially [see plate 4A of this paper], at least for the time being (pp. 91, 92).

Krompecher writing on basal-cell cancer (12) comments as follows on the subject in question:

The boundary between the carcinoma epithelium and the surface epithelium is not distinct in the greater number of the basal-cell cancers; die normalen Epithelzellen gehen vielmehr ganz allmählich in die Carcinomzellen über. Such a gradual transition where a union with the basal epithelium was demonstrably altogether objection free, I found 14 times out of 16 cases (p. 71).

Krompecher mentions especially 8 cases where there are islands of cancerous tissue around the primary tumor and says: that here any union of the carcinoma epithelium and the surface epithelium in Ribbert’s sense could be entirely excluded (p. 71).

Likewise I found in keratinizing cancers and also in the greater number of basal-cell carcinomas a gradual transition of the cell-sorts so that actually it was not possible to say where the carcinoma commenced (p. 72).

He cites other authorities against Ribbert and his students (Hansemann, Hauser, Lubarsch, Nothaft, Petersen) and says:

How plainly the strife turns about the question whether in beginning carcinoma the connective tissue or the epithelium plays a superordinate, a coördinate or a subordinate rôle (p. 77).

I must also cite Petersen since I conceive that some of his findings, like Krompecher’s, also have a direct bearing on what I shall say when I come to discuss the discrete small tumors which I have found in the pith of some of my preparations.

Petersen discusses Ribbert’s views in several long papers dealing with cancer. I quote as follows from his Beiträge zur Lehre von Carcinom (13).
On the other hand how little even the purely morphological questions of carcinoma are settled, will best be shown by the fact that seven years ago an investigator of Ribbert's importance turned everything pretty much topsy-turvy which had hitherto been accepted concerning the histogenesis and growth of carcinoma. Since then there has been a lively strife back and forth over these questions (p. 545).

According therefore to the theory of Thiersch and Waldeyer, each carcinoma begins with a disturbance of the boundary (Grenzverschiebung) between epithelium and connective tissue. Which of the two tissues causes this? Owing to the labors of Thiersch, Hauser, Hansemann and others, there is very little doubt that the epithelium is the active part: The carcinomatous growth would then depend on a fundamental change in the biological character of the epithelium, the primary cause of which remains in doubt.

Then comes Ribbert and says: Quite the opposite! The primary thing in carcinoma is always a connective tissue multiplication. This leads to the splitting off of epithelium and the epithelium thus separated from its organic union and the regulatory influence of the organism acquires the power of unlimited growth (p. 545).

Against this question of the peripheral growth of carcinoma Ribbert's opposition sets in most intensely. Here I must stop a moment to point out the fundamental importance of this question. Previous to Ribbert the growth of a carcinoma had been represented for the most part as developing, when once started, out of itself by intussusception but also growing by apposition, that is through the continuous cancerous conversion of the neighboring epithelium. The first way applied to the deeper growth, the latter to the peripheral spread of the tumor (p. 546).

With this last view Petersen agrees and shows figures to illustrate appositional growth. Of one of these figures he remarks:

In B and C of figure 2, then, the peripheral spread may be conceived as due to a cancerous conversion of the epithelium. And certainly this process must ordinarily progress continuously, so that the surface of the carcinoma always represents a fusion surface . . . . (p. 546–547).

If this proposition is true [Ribbert's view that the edges of large carcinomas are entirely unsuited for the study of the histogenesis of carcinoma and that only very small beginning carcinomas are suitable] then, as Hansemann says, the body of our histogenetic knowledge is destroyed; for what is a beginning carcinoma? Here the whole field
is thrown wide open to a subjective conception and the danger is near that a tumor which will not fit the theory is either too large, that is not any longer suitable, or too small, that is not yet suitable. This question of peripheral growth occupies, therefore, since Ribbert's first publications, always the center of the discussion (p. 549).

Ribbert's theory, at least as a whole, is not accepted by any important group. A series of microscopic observations have been brought forward as incompatible with it; against its theoretical foundations serious objections are also raised. But just as little can Ribbert's theory in its totality be regarded as set aside (p. 557).

Petersen found in his third wax model⁹ several (8 or more) small completely isolated epithelial (cancerous) islands close to the main body of the small tumor (see plates 22 to 27 of this paper) and adds:

We get in many places the impression as if originally isolated islands had united with the principal tumor during its further growth (p. 570):

One somewhat larger island was 2 mm. removed from the main tumor. The cells of these islands which, he says, are to be considered as the first metastases, are much farther degenerated than the body of the tumor. This is striking. They are horny, often more flattened with very indistinct nuclei, as if degenerating (p. 570). His fourth model is a splendid demonstration of the independent development of small epithelial cancers around the primary center. Of these he says:

The entire remaining accessory centers ("Nebenherde") c, d, e and f are completely isolated, especially e and f (p. 574).

He calls this a "reticular multicentric carcinoma" and says the changes in the connective tissue are so slight that they cannot be considered as a primary cause of the tumor. There was nowhere granulation tissue and nowhere lifting up of the epithel-

⁹ For those who do not understand this process it may be said that for a wax model a tumor is cut in series and an enlarged wax model is then made of each section indicating clearly the cancerous portion. These thin sections are then superposed one on the other and thus a model of the tumor with all of its ramifications is obtained.
Petersen says he has microscopic preparations of 330 skin cancers of which 130 were cut wholly or mostly in series. He also knows the history of all of the patients. He thinks many skin cancers (the multicentric ones) arise in hair-bulbs, sweat glands or sebaceous glands, and these independent tumors may remain independent or afterwards fuse as the tumors grow. Virchow also held this view and expressed it as follows (14):

As a rule, along with the mother tumor which may be growing slowly or not at all, at very different distances from it arise new foci which sooner or later unite with the mother nodule.

Petersen continues:

We must therefore maintain that the vicinity of a multicentric carcinoma (wholly irrespective of the cancer cells here scattered) is more disposed to a new carcinoma than remoter places.

After marshalling much evidence Petersen says:

A carcinoma in the sense of Thiersch and Hauser may arise through a primary epithelial change; the changed epithelium can grow uninterrupted in the depths; there is no need, therefore, for any "nipping-off" in Ribbert's sense.

Thiersch, who taught that carcinoma begins in the epithelium, held it probable that there is in the beginning of carcinoma a biological weakening of the connective tissue.

Petersen, who does not believe in the parasitic theory, closes his long paper as follows:

Es kann daher sowohl wissenschaftlich für die Lösung dieses dunkelsten aller pathologischen Probleme, als auch praktisch für die Bekämpfung dieser furchbarsten aller Krankheiten nur von Vorteil sein wenn von verschiedenen Seiten her und mit verschiedener Fragestellung immer wieder von neuem, trotz aller Misserfolge, unermüdlich das Studium des Carcinoms in Angriff genommen wird.
In this connection also Virchow wrote as follows at the close of his Cellular Pathology (15):

A pathological tumor in man forms in exactly the same way as does a swelling on a tree, whether on the bark, or on the surface of the trunk or on a leaf, where any pathological irritation has occurred. . . . . All of them depend upon a proliferation of cells just as abundant and often just as rapid as that which we see in a tumor of a proliferating part of the human body. The pathological irritation acts in both cases in exactly the same manner. . . . . The great importance which a knowledge of botany possesses for the pathologist also lies in this, that it enables him to discover in all these processes the existence of an inward correspondence in the whole series of vital phenomena, and to show how the lowest formations may serve to explain the history of the most perfect and complex parts.

All of which shows Virchow to have been a bigger and broader man, and a better pathologist, than some who have come after him.

Dr. Carl Ritter of the Surgical Clinic in Greifswald in 1901 (16) maintained the parasitic nature of cancer as follows:

Moreover, the whole theory that the tumor-cells are the parasite, is no explanation of the well-known facts; for the cause, whereby a [body-] cell is suddenly converted into a foreign parasite, is not in the least explained thereby (p. 175).

Ritter's strongest argument, perhaps, is that necrosis in cancer is not due to lack of blood supply but must be due to the gradually cumulative action of the products of cell-parasites. In infectious diseases the necrosis is always central and exactly so it is in carcinoma and sarcoma (p. 181). Jenny, he says, has pointed out that no one has offered a satisfactory explanation for the fact that the keratinizing process in tumors of this type is always central. Lange describes three zones in colloid cancer of the stomach, intestine, and vagina of which the outer is free or freest from degeneration, (p. 182). Ritter says all observers are agreed that the necrotic parts are central while the fresh parts with well-stained nuclei and mitotic figures are peripheral (p. 182).
Das Rätsel lässt sich meines Erachtens nicht lösen, ohne die Annahme eines fremden Virus, was an der Stelle der Verhornung diese Degeneration verursacht oder verursacht hat.

In gleicher Weise findet sich die Verkäsung und die gallertige Degeneration central, nicht am Rande . . . (p. 182).

Es geht wohl aus dem Gesagten hervor, dass die Degenerationen sich ganz ausserordentlich leicht unter der Annahme einer Infektiosität der Geschwülste erklären lassen. Diese Erklärung ist die einzige, die im Stande ist, alle Erscheinungen bei den Degenerationen zu erklären.

Ganz anders ist dies aber bei der Metastasenlehre, die mit der Annahme einer Infektion, wie es scheint, unvereinbar ist (p. 183).

Ritter’s inability to explain metastases on any parasitic basis, something not so difficult now that we know the behavior of crown gall, leads him to call them in question. His chief argument is based on “the impossibility of distinguishing by cell-form” carcinomatous tumors in other organs from tumors derived wholly from connective tissue cells. Round, or spindle, or giant cell sarcoma, or endothelioma or perithelioma, and tissues capable of producing such tumor cells, occur in every organ (p. 183).

Often an endothelioma or a perithelioma may so closely resemble a carcinoma as to be mistaken for one. A whole series of tumors formerly diagnosed as carcinoma must now be referred to endothelioma. Krompecher has shown that the most malignant tumor of the testicle is an endothelioma yet he found no such tumor recorded in literature (p. 184).

To explain gall-secretion in a lung-tumor, derived from a primary tumor in the liver, Ritter is obliged to call it a malignant adenoma and separate it from carcinoma (p. 185).

His malignant adenoma differs from carcinoma in not having the epithelium in several layers. It has no polymorphism of cells, no solid masses (Zapfen). It retains glandular structure and function, but has unlimited growth, and the metastases have the character of the mother tumor (p. 189).

Ritter makes two pertinent conclusions, patent to anyone who has reflected much on this subject: First, it is not possible
to write the pathology of a disease correctly until we know its cause; second, very likely the organism of cancer has already been isolated and neglected.

In 1899 Prof. Dr. Vincenz Czerny of the Heidelberg Surgical Clinic (17) said that sarcoma is so much like certain infectious diseases that von Esmarch suggested that all of it might be of syphilitic origin, and that actinomyces was long called osteosarcoma till Bollinger discovered the cause. He thinks it probable that many cases of malignant lymphoma and lymphosarcoma are due to modified tubercle bacilli (p. 251).

Several dozen times in his clinic when cancer of the lower lip has been excised along with the swollen regional lymph glands, no malignant cells have been found in the swollen lymphatics, only simple hyperplasia, yet in a clinical sense they were carcinomatous because, if left, there would have been a return of the carcinoma (p. 257).

Im klinischen Sinne waren diese Drüsen also schon carcinomatös infiziert, ohne dass man es schon anatomisch nachweisen konnte.

Menetrier in his excellent book on Cancer (18) takes the same view as Hauser, Hansemann et al. He says under epithelial cancer:

The increase by multiplication of its elements is indubitable. This is established by the fact that the mitotic figures are confined almost exclusively to the epithelial elements, the parenchyma, and not to the stroma; but in the extension to neighboring parts it is necessary to distinguish two possible ways: extension by transformation of like elements, and extension by substitution of cancerous cells in place of the adjacent tissues.

*Extension by transformation.* The extension by transformation is the most interesting to consider, because, even after the beginning phase of the cancer, when the latter has already considerable dimensions, something that habitually occurs in the cases ordinarily under observation, it enables us still to find and study the pathogenic process which has given rise to a malignant neoplasm.

It is through a study of the borders of the cancer that we may find the young lesions, still in formation. All authors to be exact, do not admit this concept, and among the more recent, Ribbert and Borst
energetically oppose any such interpretation; for them cancer once formed, extends of itself, without transformation of neighboring elements. "The carcinoma, on the border," says Borst, "advances with its own troops and does not add to itself new soldiers at the expense of healthy tissue."

We think on the contrary that, in a certain number of cases, the cancer not yet escaped from the tissue or the organ in which it has begun may extend by transformation of similar elements, that is of elements of the same nature as those which have given birth to it, and which are subject to the same modifying and preparatory causes of the cancerous evolution . . . . (pp. 181-182).

Concerning cancer of the stomach he says:

As we approach the cancerous ulceration we see a rapid increase in the size of the glands. They form a layer in which the thickness of the glandular tissue is such that it is really a glandular tumor, an adenoma, this, however, without the hypertrophied glands having lost the fundamental characters of their structure. Their tubular conduits are elongated so that they may be 5 or 6 times as long as normal, but their walls are not broken, their proper membrane persists, and in their interior there is a continuous covering of cylindrical mucous cells, corresponding to the type of covering normal to the glands of the pyloric region, which is the region in question.

But this epithelium is also, itself, hypertrophied, as indicated both by the length of its cells and by its vegetative tendency. This while scarcely noticeable at first shows more and more distinctly as we approach the cancerous zone (fig. 8, from A to B). In all this adenomatous zone, the thick glandular layer remains sharply limited by the muscularis mucosae.

The hypertrophied glandular layer passes over directly into a layer which is clearly cancerous, formed of an infinity of tubes, irregularly shaped, lying without order in all directions, no longer recalling any glandular structure, and lined with a cylindrical epithelium having its protoplasm quite uniformly colored throughout its length; it is the typical gastric cylindrical epithelioma, which occupies not only all the thickness of the mucosa, but extends into the depths of the subjacent layers after the more or less complete destruction of the muscularis mucosae (fig. 8C).

Between these two zones, the epitheliomatous zone and the adenomatous zone, a transition zone occurs (fig. 8D), passage from the
adenoma into the cancer, which, on the section that we have had drawn, appears to us to show phenomena strikingly demonstrative of the opinion we maintain of the continuity of the process of the adenomatous origin of cancer. At this point we see, in fact, a gland enormously enlarged in all its dimensions, hypertrophied and vegetating as to its epithelium and which nevertheless is recognizable as a gland. This appearance, moreover, grades through lesser deformations into perfectly typical glands of the region.

In its upper excretory part, the epithelial covering [of the gland] is identical with that of neighboring mucous glands, only more vegetative, as the sinuosities of its surface prove. In its deeper part, this covering, always continuous, but still more vegetative, as shown by the more sinuous line, takes on morphological appearances identical with those of the epithelium which constitutes the epitheliomatous tubes of the zone which is clearly cancerous. The gland, however, is complete, its covering is continuous, there is not any interruption of the epithelial layer, nor penetration of the epithelial masses proliferated from a neighboring region into the glandular cavities. There is no appearance of invasion of the gland by the epithelioma, but the appearance is clearly that of a transformation in place of the epithelium of the gland. Nearby, the cul-de-sacs of two glands, obliquely cut, show a similar transformation of the glandular covering, still more vegetative. And then in the cancerous zone, an epithelium provided with the same morphological characters is disposed in irregular tubes, representing a still typical but disordered proliferation, one in which the primitive glandular texture, the hyperplasicial glandular walls of the adenomatous zone, have completely disappeared.

To sum up, these lesions appear to us characteristic of a cancerous formation due to transformation of the epithelial covering of the adenomatous glands. It does not correspond to an invasion by substitution of the proliferated cancer in place of the elements of the hypertrophied glands, as some have maintained, because in no place does one see a destruction of the glandular epithelium, which would have to take place in such a case, while we actually see the transformation, in place, of adenomatous epithelium into cancerous epithelium. And in the ulterior progress of the lesion, it is the non-epithelial gland-wall, the membrane proper, the connective framework, which is destroyed and disappears, while the emancipated epithelium continues to proliferate . . . . (pp. 183–186).
This mode of extension is found also in other varieties of cancers and we obtain pictures equally demonstrative in certain skin cancers, and notably in cancers of the lips, or even in cancers of the buccal cavity, when the examination is carried out on tumors not too old or too voluminous . . . . (p. 186).

This mode of extension belongs essentially to cancers of hyperplasial, and especially of adenomatous or papillomatous origin; it is generally absent, on the contrary, in cancers of heterotopic [metastasial] origin, that develop habitually from cellular islands of very small size, which are rapidly transformed and become unrecognizable as soon as the cancer has attained notable proportions (p. 188).

Verse's statements (1908) as to the result of his researches on a wealth of material and covering half a dozen years are equally explicit. After going critically over Ribbert and Borrmann's views he comes to a contrary opinion, siding with Hauser. After examining 105 epithelial tumors in thousands of sections, he says (26):

An den Rändern älterer Karzinome kann nun eine weitere Umwandlung des Epithels vorkommen. Aber auch hier tritt die Änderung successive ein; es bildet sich erst ein cylindrisches indifferentes Epithel, aus dem durch immer weitere Proliferation die eigentlichen Karzinomzellen entstehen (p. 145).

Es ist sehr wahrscheinlich, dass die meisten Karzinome des Magendarmkanals aus Adenomen oder Polypen hervorgehen; jedenfalls ist ein adenomatöses Vorstadium anzunehmen (p. 158).


Here he is speculating and his feet are off the ground.

Lubarsch's comments are also very interesting. Of the trend of opinion among cancer specialists in 1908, which he thinks was pushed too far, he says (24):
Here we must first outline the question what sort of material we may use to investigate the histological development of cancer. As is well known, the views have changed greatly in the last 10 years, owing to the unwearyed activity of Ribbert. Previously it was believed that on the edges, even of large well-developed carcinomas, the origin of the cancer could be recognized, but this view is now as good as completely abandoned. The ruling dogma is that a cancer can grow only out of itself, that it never increases by apposition, and that only the investigation of so-called beginning carcinomas can give any idea of cancer development (p. 34).

Lubarsch wonders why Ribbert ever developed his unicentric origin of cancer since he abandoned it so soon for a multicentric origin and says:

In der Tat findet man auch in unmittelbarer oder etwas entfernterer Nachbarschaft von Haut-und Schleimhautkrebsen alle die Bilder, die Ribbert als 'beginnende Carcinome' gedeutet hat (p. 34). . . . Im übrigen scheint mir auch der grundsätzliche Unterschied zwischen dem Anerkenntnis des Wachstums von Carcinomen durch Zusammenfließen multizentrischer Primärherde und der Vergrößerung durch Apposition ein sehr geringfügiger zu sein (p. 35).

Primary adenomas and adeno-carcinomas of the liver may also arise multicentrically and grow by apposition. We know this through the beautiful researches of Siegenbeek van Heukelom of Leiden (1894) confirmed independently by many persons: Witzwicky (1899), v. Schmieden (1900), Cloin (1901), Catherine H. Travis (1902), H. Gideon Wells (1903), Weglin (1905), Polak-Daniels (1905), Horst Oertel (1905), Robert Muir (1908), Lindsay S. Milne (1909), Max Goldzieher (1910), Goldzieher and Bőkay (1911), Saltikow pro parte (1912), and many others. Ribbert and his student Heussi (1898) denied this also, very emphatically, Heussi on the findings in one liver (28). Herxheimer also denied it (1906) on the findings in another liver (22).

The substance of Heussi's objections so far as derived from his studies are given below in the first paragraph, but much more important than any of his objective findings are his theoretical objections which are given in the last paragraph and to these I would call especial attention.

But even he found three liver cells with double nuclei in the vicinity of a tumor nodule (p. 16). He also admits there are places where the boundary between tumor cells and liver cells was not sharp but attributes this to defective sections (p. 17).

Heussi also says of Siegenbeek van Heukelom:


There are no illustrations and the whole Dissertation reads like a case of special pleading in a parti pris, nor must we forget in this connection that the work was student work done under Ribbert's all compelling direction.

Heukelom's plates (19) show exquisite transitions from liver cells to carcinoma cells and both the cells and the cell-nuclei are enlarged before they become tumor cells. The nuclei of the large cells are also conspicuously notched and cleft as in crown gall.

Frohmann the same year (1894) reached the same conclusion (20):

Ein grosser Teil der Leberzellen fällt sofort durch die ausserordentliche Grösse auf (p. 10).

. . . . Was den Ausgangspunkt derselben [der Geschwulstknoten] betrifft, so lässt es sich mit Sicherheit fest stellen, dass sie ausschliesslich

Von Schmieden (29) says:


. . . . Nirgends aber lässt sich jedenfalls die Entstehung von primären epithelialen Neubildung so genau und in so jungen Anfängen verfolgen, als bei den multiplen malignen Leber-Adenomen (p. 320).

Miss Travis (31) says:

The transition from these cords to the structure of the new growth is as follows. The cells in the surrounding cords become larger, their nuclei are also enlarged and take a deep haematoxylin stain and this widened atypical strand becomes still wider, comes to have several cells abreast, and passes thus gradually over into one of the cords definitely belonging to the tumor (cf. figs. 8 and 9). . . . . The manifold small nodules scattered through the liver are then not of metastatic origin, but are primary growths derived by a direct transformation from the liver cells (p. 111).

Wells (33) writes of his liver tumor:

. . . . The small secondary nodes around the primary one seem to be formed in this way by the starting up of malignant transformation in a lobule or group of lobules a little ways from the boundary of the primary growth. But there are no secondary nodules at any considerable distance from the primary tumor. (p. 416).

. . . . This carcinoma does not seem to have grown by direct extension in the usual way, with new tumor cells crowding out the preexisting cells, but rather the existing cells themselves assume the power of proliferating in a malignant manner. (p. 416).

. . . . The independent malignant transformation of cells in the vicinity of a tumor must be of some significance. That it should be
observed particularly in the liver is, perhaps, due to the fact that the structure of the organ makes its detection simpler than it would be in other places—a similar extension of proliferation has been described in the genesis of carcinoma of the skin (Petersen) (pp. 416–417).

Oertel (34) says:


Goldzieher (37) says:

Wenn schon die in sämtlichen 14 Fällen wenigsten teilweise vorhandene morphologische Ähnlichkeit der Tumorzellen mit Leberzellen, . . . einen genetischen Zusammenhang mit dem Leberparenchym wahrscheinlich macht, so wird dies durch eindeutige Übergangsbilder wohl ganz bewiesen.

Sofanden sich wiederholt durch dass cirrhotisch vermehrte Bindegewebe abgegrenzte Leberläppchen die zentral oder peripher eine direkte Umwandlung, ihrer Zellen, in Tumorzellen morphologisch vollkommen gleichende Zellen, zeigten.

Ebenso fand sich in der Nachbarschaft eines etwa haselnusszgrössen, akzidentell gefundenen Leberkrebses, ein kleines, aus wenigen Bälkchen hochgradig entdifferenziertes Zellen bestehendes Knötchen das, wie es die Serienschnitte lehrten, nirgends mit dem gesameren Herde zusammenhang, dagegen überall in die benachbarten Leberbälkchen überging. Ebenso kommunizierten seine Kapillaren mit den anstoszenden Leberkapillaren (pp. 334–335).

. . . . The origin of the hepatocellular carcinoma is probably multicentric . . . auch durch Apposition vergrörsen können, wie es besonders in einem meiner Fälle schön zu sehen war.

. . . . The assumption of an appositional growth in Carcinoma, not everywhere accepted, it is true, although as Lubarsch has pointed out, there is no essential difference between this growth and the multicentric growth—appears to be confirmed by these discoveries (p. 335).
In opposition to Ribbert, Goldzieher continues:

More important than the separation of liver cells from their fellows appears to me to be that neverfailing phenomena of growth which was always to be observed both in the vicinity of the tumor nodules and also remote from them in the liver tissue. I mean both Hyperplasia, with the formation of small cells containing deep-staining nuclei, and Hypermotropy, that is, the production of large, very sharply-contoured [liver] cells which often contain polymorphic nuclei and which also in some cases lead to the formation of a surrounding benign adenoma of the liver associated with which is a much larger tumor, everywhere of similar origin but definitely carcinomatous (i.e. p. 336).

The next year (1911) Goldzieher and Bókay (38) expressed themselves as follows respecting their primary liver carcinoma No. 20.

Separated from the edge of the tumor by several rows of apparently unchanged liver cells, there is a nodule composed of 6 cords of liver cells the cells of which can be distinguished from the surrounding liver cells by the more abundant chromatin contents and considerable polymorphism of their nuclei, as well as by the weak basophil reaction of their protoplasm. These cords, which are not composed of 1 or 2 cell-rows like the surrounding liver-cell cords, but have 3 to 5 cell-rows are bordered by capillaries and pass directly over into the surrounding liver trabeculae, in which also scattering nuclei are visible that correspond exactly to the tumor-cell nuclei. This nodule is nowhere in connection with the larger tumor, as shown by serial sections, and did not arise as the result of capillary emboli. The capillaries are everywhere free from tumor cells, and between the cords in question, which resemble the tumor-cell trabeculae, atrophied liver cells, flattened by pressure, are nowhere to be found, such as are always to be seen even in the earliest stage of embolic liver metastases. Nothing remains therefore but to assume that here is an independent tumor in the beginning of its development, with direct conversion of liver cells into tumor cells (pp. 113–114).

Goldzieher and Bókay's observations are so interesting that I have copied their figure 10 which shows in a small primary cancer of the liver an enlargement of the liver cells on the edge of the nodule as the first stage of their conversion into cancer cells
The margin of their tumor is surprisingly like my crown-gall margins. The tumor consists, centrally, of a small area of deep-staining disoriented cancer cells, surrounded by pale-staining, big-nucleate hypertrophied liver cells, beyond which are the smaller normal liver cells. There has been no invasion here but a change in situ from normal liver cells, through hypertrophied liver cells, into cells which are definitely carcinomatous.

In 1908, B. Fischer also stated in the most positive terms that he had found multicentric and appositional growth in a primary sarcoma of the liver arising from endothelium. He writes (23) as follows:

Diese Geschwulst wächst also nicht allein aus sich heraus durch Vermehrung der Geschwulstelemente, sondern vor allem auch durch fortschreitende Umwandlung der normalen Gewebszellen in Tumorzellen. Der Nachweis dieses Wachstums lässt sich hier einwandfrei erbringen.

To return to crown gall, I am inclined to think that growth by apposition is the common form of growth in this tumor on account of the fixed place of the cells composing plant tissues. Is there then no invasion? Yes, but very often at least it is the result of appositional growth in one direction only, end to end growth, so to speak, leading to the production of an abnormal strand between other tissues. Some, at least, of the tumor strands appear to me to originate in this way. Possibly all do so. See, for example, The structure and development of crown gall. A plant cancer, Bulletin 253, B. P. I., U. S. Dept. Agriculture, 1912, plates 102, 103, where a tumor strand in the outer cortex of a tobacco stem is figured. This strand, which begins in a very shallow needle wound (crown-gall infection) at the bottom of plate 103, ends diffusely in the large-celled cortex parenchyma a little beyond the top of plate 102, as if it were growing by conversion of cells rather than by an invasion sensu strictiore, that is by wedging in between them (see also plates 17 and 18 of this paper). I cannot see that it makes any difference in the final result whether a secondary tumor develops from a migratory strand or from an appositional strand. They are both invasions but arising in mechanically different ways corresponding to physically different cell-structures.

I figured some of my earlier findings of growth by apposition in 1916 in this Journal, vol. i, no. 2, figs. 3, 4, 78, but the subject is so interesting, and so new, that it is worth while to consider it more in detail and especially to show good photomicrographs of sections from characteristic tumors so that hereafter there may be no doubt whatever as to its occurrence. This must be done whether it points toward or away from human cancers.

The first stage of the conversion of cortex-cells into tumor cells on the periphery of a growing tumor in tobacco cortex is their enlargement (plate 1B). They become considerably
larger than normal cells (plate 1A), as may be seen also from an examination of the border tissue in the planar enlargements already referred to (plates 2A, 2B and 3A). Here the number of the cells has not increased materially yet the thickness of the cortex has nearly doubled. They are not only larger than the normal cells but also they are more inclined to divide, always by mitosis so far as I have observed. On the inner margin of this area of hypertrophied cells, next to the tumor, the cells divide, as a rule, much more rapidly, that is, with unusual and very great rapidity, acquiring at the same time a greater affinity for tumor stains than the remote normal cells or than the near-by enlarged cells. The daughter-cells in this region soon divide again and again, but some of the cells are still much larger than the tumor-cells, although staining more like them than they do like normal cortex-cells. They also have thinner cross walls than the normal cortex-cells and no intercellular spaces. The nuclei of these cells are also large, much larger than those of the completed tumor-cells. It is therefore often possible to see 4 or 8 or 16 or more of these cells enclosed by the stretched and thickened wall of the parent-cell (the original enlarged cortex-cell) as shown on plates 7, 11 and 16, and still more plainly in the cells of plates 4B and 5, where they look not unlike giant sarcina-cell packets, that is, the original or parent-cells are rounded and there are conspicuous intercellular spaces between them, as may be seen in many of the photomicrographs, whereas their daughter-cells are more or less angular and without intercellular spaces. In this respect they are like embryonic tissue and also like the fully formed tumor-tissue where, ordinarily, there are no spaces between the cells. This hasty cell-division which does not allow of cell-maturity proceeds in the region of the inner hypertrophy until groups of these cells are indistinguishable from cells in the body of the tumor, either in shape, disorientation, absence of intercellular spaces, reduction of cytoplasm, size of nucleus, behavior of nucleus, or affinity for stains, i.e., until they form lobes of the tumor. Sometimes a cortex-cell does not respond to the stimulus like its fellows and is therefore surrounded and buried in the tumor tissue, where it remains unchanged, or is
crushed, or tardily undergoes division. We may conceive of the stimulus as a chemical-physical one derived from the bacteria and acting either at a distance from them, i.e., on cells in which they are not present, or as due to a direct transfer of the bacteria from cell to cell, the adjacent walls having numerous very thin places (pits) through which such a transfer might easily take place by solution of the very thin membrane, or by its rupture due to pressure, in which latter case the chemical-physical stimulus would be confined to the parasitized cells or at least would not extend beyond their immediate vicinity. These pits are shown more or less indistinctly on various plates which were not focused for that purpose, and very plainly on the wall of a dividing cell in the middle of plate 1B. In cross-section the pit-walls are only one-eighth the ordinary thickness of the cell-wall. So far as the hyperplasia itself is concerned, as distinguished from the hypertrophy, I believe it is due to direct entrance of the bacteria into the rapidly multiplying cells whereas in the hypertrophied cells we may think that they have not yet entered or, if they have entered, have multiplied only in very small numbers so as not yet to cause a great hyperplasial stimulus which comes a little later when their by-products within the cell have increased and have had time to act, a period of a few hours or a few days only. It is possible also that the bacteria act only after they are dead. The narrowness of the appositional layer (0.5 mm. or less) indicates on the whole that it must be due to the direct movement of the bacteria from cell to cell rather than to the action of chemical products at a distance from them, otherwise how explain the slight diffusion of the stimulus? This peripheral layer in process of transformation is so characteristic that from an inspection of it crown-gall can be predicted. In a way, it suggests the large-celled, large-nucleate tissue often seen in early carcinomas and held to be typical (Cullen, l.c., fig. 230, p. 441.

The fully converted cells of crown galls may be either larger or smaller than the connective-tissue cells from which they have developed. For tumor cells larger than cells of the tissue from which they have developed see my Textbook (l.c.), figures
345 and 346. Much depends on how rapidly the tumor is growing. In the case of these young tumors developed in the soft tobacco-cortex, the cells have divided many times and so rapidly that they are very much smaller than the normal cortex-cells. None of them have had opportunity to become mature or even semi-mature. They also stain very differently. The tumor tissue treated with acid fuchsin and methyl green or with haematoxylin takes a deep stain while the normal cortex with proper washing and especially if counterstained retains scarcely any of the red or purple stain. It is the protoplasm, of course, which stains. The transition tissue stains like the tumor-tissue, but paler, it is, however, easily distinguished from it by the larger and variable size of its cells and their nuclei, and often also by the surrounding walls of the parent-cells which, however, become less evident as the divisions continue and the pressure increases. Its cells are readily distinguished from normal cells not only by the formation of thin cross-walls in various directions but also by the peculiar appearance of its cytoplasm (presence of numerous granules which are plainly much coarser than those of the normal protoplasm), and by the notched, cleft or mulberry shape of many of its nuclei. These latter phenomena as well as the phenomena of mitosis must be studied under high powers of the microscope and are not distinguishable on any of the photomicrographs here shown. For notched and cleft nuclei and abnormal mitosis see The structure and development of crown gall: A plant cancer, U. S. D. A., B. P. I. Bulletin 255, Washington, Government Printing Office, 1912, fig. 1 and plate 108. The enlarged cells beyond the active transition tissue, i.e., beyond the tissue plainly in very active disordered division (plates 1B, 5 and 12), possess intercellular spaces and stain like the normal cortex-cells, that is, very feebly, if the sections are not overstained and are properly washed. That they also are in process of division may be seen from the very thin cross-walls visible in many of them.

Often the appositional growth when it is very rapid so as to produce great pressure comes to an end suddenly by the crushing of remoter tissues (plates 3B, 4B, 8, 9, 10), and occasionally
it ends abruptly in some part of a tumor for no plain reason, in which case the cells are flattened from the pressure but not crushed (plate 4A).

The most striking thing perhaps in these tumors, aside from their growth by apposition, is the rapidity of their growth and the correspondingly small size and great immaturity of their cells. Indeed, it is one of the most remarkable things I am acquainted with in biology that a schizomycete should have such power to change the behavior of a cell without destroying it (see Ribbert's dogmatic counter statements, cited on page 8). The tumor-cell is often only from $\frac{1}{20}$ to $\frac{1}{50}$ the size of the cortex-cell from which it has developed (I am thinking here in 3 dimensions). Only the nucleus retains something like its former size and consequently nearly fills the cell leaving but scant room for the greatly reduced cytoplasm. The nucleus of the tumor-cell in these tobacco—cortex tumors is actually reduced in size, i.e., smaller than that of cells in the transition tissue but is not reduced proportionately to the cytoplasm, nor anything like proportionately. In the tumor, roughly speaking, $\frac{1}{15}$ of the cell-space on cross section is occupied by the nucleus. In the normal cortex-cells, in the middle of the bark, the nucleus occupies only $\frac{1}{50}$ to $\frac{1}{150}$ part of the whole area of the cross-section. In general, I believe it is safe to say that there is 100 times as much nuclear substance per cubic millimeter in the tumor-tissue as in the normal cortex, out of which it has developed, and sometimes much more, but considerably less than in an equal volume of embryonic tissue, developing roots for example as on plate 28. This fact of cell-immaturity, of greatly reduced cell-size and of relatively greatly increased nucleoplasm, together with absence of intercellular spaces and exhibition of great affinity for protoplasmic stains, is characteristic and makes the tumor-tissue somewhat resemble embryonic tissue, yet it is not embryonic tissue. It does not grow as rapidly, its nuclear substance is less abundant, its cytoplasm is more granular, its reaction to stains is somewhat different (less deep and slightly different in tone), its cells are less normally oriented, and finally it has neither the persistent vigor nor the totipotent power of the
embryo. It cannot produce out of itself the whole plant or any organs of the plant but at most only a stroma of cells and vessels, and even this in many cases, and probably in all, arises out of the normal tissue pari passu with the round-about development of the tumor-cells, yet if totipotent cells or pluripotent cells are in its vicinity, or borne on its surface, or surrounded by it, the stimulus of the tumor sets them growing and then we may have a tumor full of fugitive shoots or roots or flower buds or tiny buried fragments of organs, that is, an embryoma. Root-anlage outside of a tumor, but near it, are very often set growing as shown on plate 28 at R and shoots behave in the same way. Any cancer-specialist who has worked much on embryonic tissues knows that they are quite unlike tumor-tissues, even when they occur exposed to them as tiny fragments in solid embryomas. This to my mind makes it unlikely that dislodged embryo-cells or misplaced tissues of any sort are the origin of malignant tumors. They may begin in such tissues—but why? I am quite of the opinion of those oncologists who maintain that the cancer-cell is a biologically changed cell; only in case of human and animal cancers we do not know what causes this change, whereas in crown galls we know that it is due to an intruding intra-cellular schizomycete.

Within the nucleus of the tumor-cells the nucleolus is often surrounded by a clear space which is very conspicuous, much more so than in normal resting nuclei but this may not be pathological. The nucleus also is often deeply and sometimes repeatedly notched or cleft even to complete division. This has been seen in the smallest tumor-cells in the center of these tumors but it occurs more especially in the actively dividing cells of the transition tissue on the margin of the tumors, that is, in the youngest part of the tumor. Here many nuclei are notched and cleft, and sometimes entirely divided, but whether this is wholly abnormal or follows the law of growth of tobacco-cortex under special conditions, i.e., whether it can occur in the absence of tumors where growth is very rapid; and whether in the peripheral growth of these tumors the cell-division is wholly mitotic or both mitotic and amitotic must be left for further research.
I have seen cells in mitosis in the center of these tumors and spindle-figures in cells of various sizes on their periphery both in the actively changing part and in the hypertrophied cells outside of this part. So far as I have observed, however, mitotic figures are rare in all of these 15 tobacco-cortex tumors, i.e., less than one per field of the microscope. This might mean either that growth was slowing down or only that the material was collected at the wrong time of day. All of the material was removed and fixed in the middle of the afternoon and it is assumed that most of the karyokinetic cell-divisions occur at night since we know that in many plants most of their growth occurs at night. From examinations of many sections of Paris daisy tumors made in my laboratory in 1911 from material fixed every hour throughout the night, as compared with sections of many tumors fixed in the daytime, it is plain that most of the cell-divisions in that tumor occur at night.

Not infrequently in the tumor-tissue and also in its vicinity two nuclei occur in a cell without any trace of a wall between them. On the periphery of a tobacco-cortex tumor in one of the larger cells I observed four well developed nuclei with no trace of any cross-walls even the most delicate separating them. Miss Lucia McCulloch and Miss Nellie A. Brown of my laboratory both observed and sketched the same thing in 1911 studying the night development of crown gall on the Paris daisy.

These tumors are so young that necrosis has not appeared in them anywhere, the only dead parts being certain crushed cells just beyond their borders, but when necrosis does occur in crown galls it begins centrally.

The two inoculated tobacco plants which furnished the material for this paper bear the numbers 1548 and 1549 and the various independent tumors on each are designated A, B, C, D, etc. All these tumors are of the same age (three weeks) except the small pith tumors, which I must think are secondary, and very young, probably not more than a few hours old, in case of the smaller ones (plates 25 and 26). All were produced by single needle pricks without hypodermic injection and consequently the primary infection was only in the cells wounded by the needle thrust.
All of the sections were stained in the same way, viz., several hours in 1 per cent Grübler's methyl green dissolved in distilled water, for the lignified tissue, which is stained blue; then, for a few minutes only, in 1 per cent Grübler's acid fuchsin dissolved in 70 per cent ethyl alcohol, for the tumor-tissue, which becomes red. After this they were washed and dehydrated by passing them very quickly through 85 per cent, 95 per cent, and absolute alcohol, after which they were passed through xylol and mounted in Canada balsam.

For further details the reader is referred to the plates. First an enlarged cross-section of the normal young cortex is given showing the type of cells wounded and what is assumed to have been the deepest wound inflicted. From this it will be seen that the deeper cells of the tobacco-cortex are larger than those near the surface, but this has made no difference in the result, many of the smallest tumor-cells having been derived from the large cells of the cortex rather than from the small ones. Then are given some low-power (× 20) planar views of sections from several of these tumors. After which follow, in medium enlargements (× 93 or × 205), photomicrographs of the margins and deep parts of various tumors cut in different planes. In one case (tumor 1548A) I have made a series of photomicrographs at different levels (see fig. 3) from near the center of the tumor on slide 7 to beyond its margin on slide 12. These are 20μ sections and the total distance traversed is 1660μ but in the fresh material of course, considerably more than that. The sections on slides 9 and 10 in this series are particularly instructive as may be seen from plates 6 to 8. Here the knife has passed parallel to the surface of the tumor in its extreme outer part or just beyond it (appositional layer), and there are striking exhibitions of transition tissue. In fact, on plate 7 the whole center of the plate shows normal cells in process of conversion into tumor-cells. On plate 8 may be seen the lower part of plate 7 (X corresponding to X) and here also the remoter hypertrophied layer, beyond which are normal cells. On slide 12 in this series we pass beyond the tumor but not entirely beyond its influence. For sections of the borders of other tumors passing through the
whole thickness of the appositional growth, i.e., cut at right angles to plate 7, see especially plates 9 to 13.

In all or nearly all of these tumors the vascular cylinder has been split open by the growth of the tumor (plates 18 to 21) and the pith is in process of invasion. For the latter phenomenon see plates 23 to 27, together with figure 4 which marks the location of the various sections from which the plates were made. In 1548D in the outer pith, beyond the advancing margin of the main tumor and close to the inner edge of the split wood, are various scattered small tumors (see plate 22 for orientation). I have not been able to connect back these small pith-tumors.
APPOSITIONAL GROWTH IN C.-G. TUMORS AND CANCERS

definitely to the cortex-tumor by any strand of tumor-tissue
and in this way they are like Krompecher's and Petersen's small
tumors, arising independently in the vicinity of a mother car-
cinoma, as Petersen showed quite clearly by his wax-plate method.
I have not applied this method but from a study of the serial
sections I do not think it is possible that all may be connected
by cell-bridges, even the tiniest. At least this is not evident.
They appear to be metastases but they are not such in the true
meaning of that term, and neither perhaps were Krompecher's
or Petersen's, but if I am right in the explanation which follows
as to their origin, then perhaps they might be designated pseudo-
metastases.

Recently I have gone over all the serial sections again and can
only conclude that while these small tumors are near the parent
tumor and in tissue somewhat like regeneration tissue, devel-
oped in response, probably, to the wedging open of wood and
pith by the continued deep growth of the primary tumor, they
are not actually part and parcel of the mother tumor, but all
would undoubtedly have fused with it a little later. In one
instance a small tumor lies rather deep in the pith—a whole field
of the microscope away from the inner wood, that is, about
half a field farther in than the tumor on plate 24—and this
appears to have developed from the proliferation of a few small
pith-cells, making of it an irregular fine-celled, deep-staining
strand between large pith cells. It contains only a few hundred
small tumor-cells surrounded on all sides by pith cells. This
tumor strand begins on slide 16 and ends on slide 23, and I have
not been able to connect it with any of the discrete small tumors
already mentioned or with the primary tumor. Here also I
saw conspicuously notched and cleft nuclei, both in the tumor
tissue and in the pith cells immediately surrounding it (slide 19).
A similar isolated strand containing a few hundred cells only is
shown on plate 27. This begins on slide 12 and ends on slide
14. Four of the smallest crown-gall tumors I have ever seen are
shown on plates 25 and 26. They represent relatively few cell-
divisions (disoriented, large-nucleate and deep-staining, be it
observed) and cannot be more than a few hours old.
We may suppose these small pith tumors, if they are really secondary, originated in this way; that during the tearing open of wood and pith, resulting from the rapid growth of the primary tumor, certain of its infected cells were crushed liberating into the wounded wet area some of the motile rods of the parasite which then made their way through intercellular spaces or fissures into a few of the torn pith cells along the line of the rupture, converting these cells into a dozen or more new centers of tumor growth.

For further consideration see the plates and the accompanying descriptions.

In many of these sections, as in some of those from the Paris daisy tumors (see An introduction to bacterial diseases of plants, W. B. Saunders Company, Philadelphia and London, figs. 353 and 354), there are in the same tumor two types of tumor-cells, a spindle-cell originating from cambium and an ordinary round-cell of variable size derived from the cortex. The spindle-celled tumor tissue occurs not only in the deep parts of the tumor, near the ordinary cambium, but also in the outer parts of the tumor as if derived from incipient cork cambium, but I have not been able to trace the origin of the latter very clearly.

What resemblance, if any, the phenomena here described may have to peripheral growth in animal and human cancer must be left for the oncologists to determine. As we have seen from the statements cited in the first part of this paper, students of cancer are poles apart in their views as to how primary cancer grows in tissues of its own type, but it will be observed that there is a wide difference in the value of the two kinds of statements since the one kind are affirmations based on observations while the other are denials based on inability to see. I do not take Ribbert's statements seriously, because I do not regard Ribbert and his school as biologists at all but only as morbid anatomists and the solution of the cancer problem must come I think, from experimental biologists. In this connection it might be well to remember that when a man approaches a problem with a preconceived notion he is often as blind as a bat to the plainest phenomena. Every experimenter knows this from his own
observation and not infrequently from his own experience. One of the important things to be settled, it would seem is whether anything like what I have here described occurs in human cancer. Hauser, Hansemann, et al., say it does; Ribbert, Borst, et al., say it does not. If it does occur, then it is one of the strongest evidences pointing toward parasitism and it does not need to occur always to be important, nor need it be in any way confused with invasion, which is the entrance of the cancer cells into tissues of other types where in general no claim is made that there is any growth by apposition (see views of Hansemann and others cited in this paper).

SUMMARY

In addition then to (1) the absence of any capsule and conversion of cortex-cells into tumor-tissue by contact (growth by apposition), something easily to be understood in this tumor because it is due to an intracellular schizomycete and the adjacent cellulose walls of the cortex-cells, ray-cells and pith-cells are numerously pitted and are fundamentally all one type of tissue, the photomicrographs show a number of other interesting features; (2) the frequent limitation of the appositional growth through the crushing of remoter cells of the cortex; (3) the limitation of peripheral growth on one side or lobe of a tumor for no apparent reason while it continues on the other side or lobes; (4) the penetration of the tumor by way of the medullary ray across the phloem, cambium and the woody cylinders which are split apart (5) the formation in some cases of independent small tumors (pseudometastases) in the pith near the primary tumor although the inoculations were restricted to the cortex; (6) the downward invasion of a medullary ray (beginning of a tumor-strand) in the wood as shown on plate 17; (7) the small size and immaturity of the tumor-cells in comparison with the size and age of the mother-cells and their great affinity for tumor-stains, as may be seen by the contrast in color of the normal and abnormal parts on the photomicrographs, the deeply stained parts of the sections having photographed dark and the pale parts light; (8) the enormous multiplication of cells considering that the tumors
were produced by single infected needle-pricks and that the whole period of growth was only three weeks; (9) the absence of any intercellular spaces in the tumor tissue or in the rapidly dividing transition tissue; (10) the distinct enlargement of the cortex-cells before their conversion into tumor-cells, which leads to a thickening of the cortex around the tumor, as shown on the plates already referred to, a sort of cushion being formed of which the tumor is the center; (11) the tendency of the nuclei in the transition tissue to be large and to be variously notched, cleft, lobed, or mulberry-shaped and the occasional occurrence of 2 to 4 nuclei in the cell; (12) the big border around the nucleoli, perhaps only indication of rapid growth; (13) numerous faint-staining abnormal granules in the cytoplasm of the transition tissue and of the tumor tissue as seen under high powers; (14) the fact that in young plants (those less than half grown) almost any cortex-cell is capable of further and repeated division, especially under a tumor-stimulus, whereas results on old tissues tend to confirm Bard's view that the reproductive capacity of old cells is zero; (15) development of roots under and near the tumors as a result of the tumor stimulus; (16) experimental disproof of Ribbert's dictum that parasites cannot change the form of cells or cause them to proliferate. Schmieden's words respecting his liver tumors describe the hypertrophy on the margin of these crown galls exactly: aus diesen Riesenzellen wachst unmittelbar eine Brut hervor, die keine Leber [Cortex]-zellen mehr sind, sondern Zellen des Tumors.

RECAPITULATION

The collateral enlargement on which the tumor rests, is both a hypertrophy and a hyperplasia. It has three stages of development; it is first a hypertrophy, then an accessory hyperplasia, and finally on its inner face it becomes part of the tumor itself.

[All the photomicrographs here shown were exposed and developed by the writer, but the prints for the half-tones were made by James F. Brewer. The serial sections were embedded, cut and stained mostly by Helen Fox, but a few by Lucia Mc-
Culloch. The photomicrographs were made on Cramer's Iso slow plates, except plate 20 which was made on a Seed's no. 30 Gilt Edge plate. All were made without use of color screens.

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(22) Ziegler's Beitrage, 16ter Bd., Jena, 1894, pp. 341–387, 2 pls. in color.


developed (p. 275). The adenoma showed a decided inclination to malignancy, although he could not find, as Schmieden did, transitions to adenocarcinoma (p. 276).


[The part relating to primary cancer of the liver deals with 6 cases.]

"In these six cases the origin of the tumor from liver cells is undoubted. In all of them the cells of the growth are in places closely similar to liver cells, and in five of them direct continuity with the liver columns can be traced at places, the appearance indicating multiple foci of origin (p. 299).

The origin of the growth in all cases is from the liver cells. . . . .

The cancer takes origin in multiple independent foci. In many of the small nodules direct continuity with the liver columns can be seen. The conclusion seems inevitable, that these young nodules are not secondary but are fresh foci of growth. (Summary, p. 302.)"


In the other 14 cases the tumor cells greatly resembled liver cells.


PLATE 1

1A. Young (stained) tobacco cortex in plant 1548 near tumor A, but not influenced by it. Epidermis at right. All of the cortex is included except 2 or 3 rows of cells at the left. The type of inoculation (needle-prick) is also indicated and the results show that many of these cells were young enough to proliferate. At this level very few nuclei are visible, but more were visible at a slightly different level. Very few of the cells are in process of division. Slide 1548 A 4, lower row, sixth section from left. 8 mm. 4. c. Bellows 40. × 205.

1B. Slide 1548 D 5, lower row, fourth section from the left showing in cross-section hypertrophied cells bordering on the tumor which is one field of the microscope (8 mm. 4 oc.) away from the center of the photomicrograph in the direction of the arrow. Several of the cells show pits (thin places) on their walls. The wrinkling of the walls is due to shrinkage during fixation. Nuclei out of focus are shown at X, X, and the intercellular spaces are very distinct. The bottom of this plate joins on to the top of plate 5. × 205.
PLATE 2

2A. Cross-section of tumor 1548 D showing various lobes resulting from appositional growth. Pith at extreme bottom, right side, vascular ring invaded and ruptured with beginnings of tumors in the outer pith; cortex thickened on either side of the tumor and its cells enlarged. Growth by apposition was still proceeding. Slide 10, top row, third section from the left. Planar 35 mm. Bellows at 58. × 20.

2B. Cross-section of tumor 1549 D. Cortex above and pith at bottom. Shows splitting of the vascular ring (center) and thickening of the cortex near the tumor with enlargement of its cells. Growth by apposition is present on both sides. Slide 16 (which passes through about the middle of the tumor), top row, first section at left. Planar 35 mm. Bellows at 58. × 20.
PLATE 3

3A. Cross-section of tumor 1549A. Unfortunately most of the wood (X, X) was removed before it was embedded. Vascular cylinder invaded and split open, cortex thickened and its cells enlarged on either side of the tumor. Slide 7, top row, last section at left. Planar 35 mm. Bellows at 58. × 20.

3B. Tangential section of tumor 1549 I (tangential to the stem). Lobate tumor in center surrounded by cortex. Needle prick at X. Growth of tumor stationary above or nearly so; marked appositional growth in progress on the sides and below. There is also crushing of tissues two-thirds of the way around the tumor where the growth-pressure has been greatest (for details see plate 4). Slide 12, top row, second section from the left. Planar 35 mm. Bellows at 58. × 20.
PLATE 4

4A. Same tumor as in plate 4B (1540 I), but from the other side. The cut is tangential to the stem. Here growth has ceased or nearly ceased, the tissue is not crushed, and the tumor-tissue abuts on pressure-flattened and slowly dividing but otherwise nearly normal cortex, i.e., there is not much evidence of conversion by apposition here, but there is a little (at the bottom right and in the middle left part), and of course there may have been much more earlier and might have been later. Slide 11, upper row, last section at right. 16 mm. 4 oc. Bellows at 40. × 93. For orientation see plate 3B.

4B. Tangential section of tumor 1540 I. Lobes of tumor tissue at top, transition cells of various sizes in middle with crushed tissue on the outer border (Cr) beyond which at the right are 3 rows of unchanged small cortex cells and the epidermis (e). Notice the dyad and tetrad groups of cells in the transition tissue. Slide 12, top row, 3d section from the left. 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 5

Tumor 1548 D, slide 5, lower row, 4th section from the left, showing stretched cells at the top, some of which (cc) are dividing and below these more actively dividing transition tissue bordering on the tumor. In the middle are 3 rapidly dividing cells in a row, with the wall of the parent cell well preserved; nuclei are visible in these cells and half a dozen faint cross-walls. Below at the left also is a stretched cell with two delicate cross-walls, C, C. Pits on wall of a cell at P. The surface of the stem is in the direction of the arrow. 8 mm. 4 oc. Bellows at 40. × 205.
Cross-section of tumor 1548 A, made close to its surface, especially in the central and upper part of the figure. Wood and phloem in upper left corner. Tumor cells in center and at right. The section cuts deeper into one of the tumor lobes in the lower right corner than elsewhere. Transition tissue at left from top to bottom, i.e., deep cortex-cells being converted into tumor-cells. Special attention is called to the middle of this figure, for comparison with the next plate.

The black dots are deep staining nuclei. The center of this plate covers exactly the center of plate 7 but is 300 μ nearer the great mass of the tumor, i.e., while tumor-cells occur in the center of this section, in the same region on slide 1548 A 10 (see plate 7), we have only transition tissue, in other words, there we are beyond the tumor proper (except one lobe of it in the lower right corner) but in cortex-tissue which is becoming tumor tissue. For orientation consult figure 3, sub 3. Slide 9, top row, 3d section from left. 16 mm. 4 oc. Bellows at 40. X 93. The center of this tumor which is found on 1548 A, slide 7 (Fig. 3, sub 1) shows invasion of the wood.
PLATE 7

Cross-section of tumor 1548 A, but 300 \( \mu \) (fifteen 20 \( \mu \) sections) farther out than plate 6. For orientation see figure 3, sub 4. Vascular cylinder in the upper left corner, a lobe of tumor-tissue in the lower right corner. All the tissue between is cortical tissue becoming tumor tissue and may be compared with plate 1A, making some allowance for difference in magnification. For the same section about one-half field at the left of this field, see plate 8. Tumor 1548 A, slide 10, top row, second section from left. 16 mm. 4 oc. Bellows at 40. \( \times 93. \)
PLATE 8

Cross-section of tumor 1548 A 10. Same section and same orientation as plate 7, but a little farther to the left, X in this plate corresponding to X in plate 7. Normal cortex at left, enlarged cells in the middle, rapidly dividing transition tissue on the right (above) then crushed tissue with tumor tissue below, which is black because the plate was under-exposed for this deeply red stained part in order to bring out more clearly the cells above it. Torn vascular cylinder at the top. 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 9

Cross-section of tumor 1549 A. Tumor tissue (t) at bottom, rapidly dividing transition tissue (tr) in middle with 3 or 4 different sizes of cells, then stretched and crushed tissue (Cr) and beyond this, enlarged cortex-cells, those at the right in division. Contrast size of nuclei in t and tr. Epidermis at E. Slide 10, middle row, 4th section from the left. 16 mm. 4 oc. Bellows at 40. X 93.
PLATE 10

Cross-section of tumor 1540 C. At bottom, tumor-tissue (t); in the middle transition cells (tr) of various sizes bordered by crushed cells (cr); at the top, cortex on the right and vascular tissue (xy) on the left. Epidermis at E. Slide 24, lower row next to last section on the right. (For opposite margin of this tumor see plate 11). 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 11

Same tumor (1549 C) and same section as on plate 10, but from the other side. Tumor cells (t) at the top, transition tissue in the middle (from A to B), unchanged cortex at the bottom. Surface at S and, under this, spindle-cells mentioned in the text. In places in the transition tissue the stretched outline of the original cells can be made out owing to the enclosing older thicker cell walls, the daughter cells being angular and having no intercellular spaces. The actual diameter of the transition tissue in this section is 1/2 mm. and as in the preceding there is a very good gradation from transition tissue into tumor tissue. 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 12

Cross-section of tumor 1549 D. Tumor tissue at bottom (t), rapidly dividing transition tissue in middle (tr), at the top stretched cortex cells dividing more slowly. At C, C, are delicate cross-walls in the stretched cells. The round dark bodies are nuclei. Pits in the cell wall at P. Observe intercellular spaces between the stretched cells and absence of them in the tumor tissue and in the rapidly dividing transition tissue. Surface of stem in direction of arrow. Only about 1/20 of the tumor area is here shown. Tumor due to a single needle-prick, time 3 weeks. Slide 24, top row, 4th section from the left. 8 mm. 4 cc. Bellows at 40. X 205.
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PLATE 12

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PLATE 13

Same tumor (1549 D 24), same section and same orientation as plate 12, but one field of the microscope nearer to the vascular cylinder. Tumor tissue below; transition tissue of several cell sizes dividing rapidly in the middle; stretched and more slowly dividing cortex cells at the top, divisions at C, C, pits on cell walls at P, outer phloem on the extreme left at X, X. 8 mm. 4 oc. Bellows at 40. × 205.
PLATE 14

Cross-section of margin of tumor 1549 D, showing tumor-tissue with very conspicuous nuclei, transition tissue at t, t, where the nuclei are largest and a stretched cell at X. Pits on cell wall at P. Surface in direction of the arrow. Slide 21, upper row, first section at left. 8 mm. 4 oc. Bellows at 40. × 205.
Cross-section of the margin of a lobe of the tumor 1549 D, showing stretched cells some of which are buried in the tumor tissue. These stretched cells have formed delicate cross-walls at C, C, and the nucleus is visible in a number of the segments. At P pits on the wall of a buried cell. On this side of the tumor in this section growth is slowing down but on the other side there was rapidly dividing transition tissue, and on this side also at a different level, as may be seen on plate 2B. Tumor 1549 D, slide 25, top row, 5th section from the left. 8 mm. 4 oc. Bellows at 40. X 205.
PLATE 16

Undulate margin of a lobe of tumor 1549 D on slide 22, bottom row, second section from the left. The section, cut tangentially, shows lobules of tumor tissue mingled with transition tissue. At the top there are stretched cells. In the center the outlines of some of the original stretched cells are still visible although they have divided several times. Under P pits are visible in the wall of a cell. The arrow points to the surface. The bulk of the tumor is in direction of the two arrows. This section is near the surface of one of its lobes. 8 mm. 4 oc. Bellows at 40. × 205.
Tangential section of deeper part of tumor 1549 I, that is, a section from slide 17 (top row, 3rd section from the left), passing through the wood. Middle, at the top, tumor tissue breaking across the vascular ring; under this the tumor stimulus is propagating downward in a medullary ray (M), i.e., here is the beginning of a tumor strand. The two medullary rays at the right of this are also not exactly normal, i.e., their cells are beginning to divide. The tracheids tr, tr, are also disturbed, that is a tumor stroma is beginning to form. 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 18

Photomicrograph from tumor 1549 D, slide 13, top row, third section from left, showing a wide medullary ray (M) due to appositional invasion of the tumor. Tracheids in cross-section at X X. Normal medullary ray at N. Most of the others are more or less abnormal. This is a much earlier stage of invasion than that shown on plates 19 and 21. The surface of the stem and the bulk of the tumor are in the direction of the arrow. The enormous number of pits on the tangential walls of the ray cells would seem to greatly favor the inward movement of the tumor impulse. 8 mm. 4 oc. Bellows at 40. X 205.
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PLATE 18

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PLATE 19

Cross-section of tumor 1548 A, slide 7, lower row, last section but one at right (see fig. 3, sub 1) showing a wedge of tumor tissue separating the vascular ring. The wedge is wider and pushes in farther on other sections. A vertical section of this wedge along the line indicated (X—X) or rather somewhat deeper would have resembled the upper part of plate 17. 16 mm. 4 cc. Bellows at 40. × 93.
PLATE 20

Cross-section of tumor 1549 F, slide 9, lower row, last section at right. Field showing fan-shaped aggregation of vessels (tracheids) at either side of a mass of fine-celled tumor tissue in what may be assumed to be the region of the needle-prick. These tracheids are part of the stroma but I assume them not to be direct outgrowths of the tumor-cells but to have been laid down out of normal tissues early in the development of the tumor, that is, soon after the needle-prick was made. The middle outer surface of this tumor (region of the needle-prick) is just beyond X. Several other tumor lobes are visible (t, t, t). The photograph does not give the contrast of the stains because the tumor cells are red and the tracheids a bright blue. 16 mm. 4 oc. Bellows at 40. X 93.
PLATE 21

Cross-section of inner part of tumor 1549 G, showing the tumor-cells wedging apart the wood-cylinder. The cambium line is at C, C, and the entire width of the tumor wedge in the cambium region is about 1 mm. Slide 4, lower row, last section at right, 16 mm. 4 oc. Bellows at 40. × 93.
PLATE 22

Cross-section of tumor 1548 D at its inner edge (right side of plate) showing tumor wedge in the wood in the middle of the right side (pt) and several incipient discrete little tumors in the outer pith (middle and left side). Slide 9, top row, 2d section from the left. 16 mm. 4 oc. Bellows at 40. \times 93.
PLATE 23

Cross-section of tumor 1548 D, i.e., the same subject as plate 22, but more highly magnified and from slide 6, lower row, 4th section from the left, to show a small nodule of tumor tissue in the outer pith. At the top and left side of this tumor there are flattened cells (F, F, F) and crushed cells (Cr). Tumor-cells are visible also at X. The fine-celled tissues at S, S; are groups of the inner sieve tubes in cross-section. The wood-cylinder is in the direction of the arrow. The main tumor shown here begins on slide 3 and runs out on slide 9, and I was not able to connect it with the primary tumor by any tumor-strand or tumor-cells, but it is not far from other smaller tumors which are nearer the main invading mass; nor was I able to connect the strand-like tumor at X either with this tumor or with the primary tumor. It begins on slide 6 and runs out on slide 8, but some other small tumors appear on sections of that slide above and at the right of this area (See plate 22). This is the only instance in which I observed tumor tissue growing beyond the crushed tissue (above the upper Cr). 8 mm. 4 oc. Bellows at 40. X 205.
PLATE 24

Same primary tumor (1548 D) as plate 23 and from same general locality, that is, the outer pith, but from slide 15, upper row, third section from the left, i.e., 20\mu (101 twenty \mu sections) intervene between this section and the one from slide 6 (plate 23). The whole 2 mm. thick region is more or less cancerous, i.e., several tiny tumors are scattered about in the pith, and between these and the body of the primary cortex-tumor there are others in the repair tissue in the region of the inner wood along the line of the primary invasion but they are not connected with each other or with the primary tumor as far as I can determine. At the right, at S, S, S, and X, as on plate 23, are groups of sieve tubes in cross-section. Below the principal nodule are smaller groups of tumor cells (at t, t) and there appear to be some deep-staining tumor cells mingled with the sieve tubes at X, but these are all confined to a few sections. The large cells are pith-cells unchanged below especially at the left but flattened above by pressure and dividing. At P P, pits are visible on cell-walls. This tumor (the larger one) begins on slide 14 and ends on slide 15 (there are twelve 20 \mu sections on each slide in this series) and I cannot connect it back to the primary tumor by means of any tumor-strand, although like the preceding tumor (plate 23) it is not far from the main tumor-mass. In this connection it should be remembered that \textit{Bact. tumefaciens} is a motile organism and that it might perhaps reach and enter particular cells just beyond the margin of the primary tumor through rupture of tissues as indicated in the text, in which case discrete small tumors (pseudometastases) would be produced and a chain of tumor-cells would not be developed. 8 mm. 4 oc. Bellows at 40. \times 205.
Tumor 1548 D, slide 8, lower row, 2d section from the left. In the center are two small tumors (t, t) in the ruptured area close to the inner wood (which is on the right side in cross-section); tumor tissue also occurs at t'; sieve tubes at S, S'. The sieve bundle S', and the tracheids tr, are on the margin of the rupture and are undisturbed. The sieve tubes at S are pushed in. At st are vessels separated from their fellows (x, x, x, tr). Beyond the arrow (about 1-1/2 inches at this magnification) lies the tumor shown on plate 23. Twisted (disturbed) tracheids of the inner wood at XXX. These tumors begin on slide 8, and end on slide 9. Two others in the same relative position but from slide 14 are shown on the next plate. 8 mm. 4 oc. Bellows at 40. X 205.
PLATE 26

Tumor 1548 D, slide 14, lower row, 3d section from the left. Same orientation as plate 25. In the center in the ruptured area are two small tumors (t, t) at the junction of wood and pith. These tumors begin on slide 13 and end on slide 14. At \( X \) in the inner wood is the advancing margin of the primary tumor. At \( st \) are separated vessels; at \( tr \) the vessels are in place. A vessel just beyond the upper \( st \) (out of this field) is crushed by pressure. 8 mm. 4 oc. Bellows at 40. \( \times \) 205.
PLATE 27

Tumor 1548 D, slide 14, top row, 3d section from the left. Deep staining, strand-like small tumor in pith, just above the central tumor of plate 24. It begins on slide 12, and ends on slide 14. Another group of tumor cells at t'. The surrounding pith cells are under pressure (flattened) and are beginning to divide. Inner sieve tube region at S, S, S. 8 mm. 40 c. Bellows at 40. × 025. The half-tone does not keep the contrast of the photograph or of the stained section.
PLATE 28

Cross-section of tumor 1549 E. Deep tumor tissue (lower right) and transition tissue in middle and on the upper right; outer part of the vascular ring on the extreme left and arising from it, at $R, R$, two incipient roots stimulated into development by the growth of the tumor. Slide 9, top row, 2d section from the left. 16 mm. 4 oc. Bellows at 40. $\times$ 93.