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THE VIRUS TUMORS AND THE TUMOR PROBLEM[1]

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NOT long ago, in the dark ages of medicine, one could think nearly anything about disease because one knew almost nothing. Theoretical system succeeded system, from humours to homeopathy. Opinions strongly held appeared like realities and were acted upon as such. Now for most diseases all this is at an end: fact has killed fancy. Not as concerns tumors, though. Knowledge of these is still so fragmentary that the mind can play at will, devising explanations as in the bad old days: the tumor problem is the last stronghold of metaphysics in medicine. But it is a stronghold closely besieged. Each new physical, chemical or biological discovery is brought to bear upon it; and whereas formerly the doctor asked himself what this or that idea might mean for the tumor problem, now he is increasingly enabled to ask what this or that fact means. I will treat here of facts which show certain tumors to be due to viruses and will deal with the implications of this knowledge.

Let us glance first at the general progress toward an understanding of the neoplasms. Since the turn of the century men have recognized that animal tumors provide an abundant material for studies of the general problem; and they have succeeded by transplantation in perpetuating many of them for experimental purposes. Already familiar with the immense world of tumor morphology, they have worked out the laws regulating tumor growth; they know something of the chemistry of the neoplastic cell, and a good deal about hereditary factors in the incidence of cancer. Taking pattern from nature, they have learnt how to

[1] Lecture delivered December 5, 1935.

induce tumor formation at will, through the action of various agents on the tissues; they have purified or synthesized some carcinogenic substances, and by investigations of their structure have taken a first step toward understanding how they act.

Some old hypotheses on causation have gone down before the new findings but others have taken their place. Whereas formerly such hypotheses derived from observations on spontaneous tumors as they ran their course in the individual, now they are largely the outcome of studies on strains transplanted through host after host, often for periods equal to many lifetimes. Such growths offer a controlled material for experimental tests but a dubious basis for thoughts on causation, since they are not representative of tumors in the natural state.

The neoplastic cells of a "spontaneous" tumor, though all derived from the same tissue and of the same general character, may differ not a little individually, in special when they are malignant. As they multiply in the original host, a continual selection of optimum conditions goes on, with result frequently in increased rapidity of growth, progressive disorder and anaplasia. On transplantation to another animal new influences come into play, compatibility being paramount, and ultimately through their action all those cells are suppressed which are not fitted to survive the foreign conditions. Usually in the course of passage through a few hosts most of the natural variety of the growth is left behind, and it comes to consist of standardized parts, so to speak, of malignant cells remarkably like one another, with a supporting stroma. The tumor is now to all appearance a stable entity, the same in host after host, with little of the cell variation that may have been present in the growth from which it stemmed. In the lack of knowledge of the spontaneous neoplasm from which the growth came, one might readily overlook the process of gradual, unnatural selection that has been going on, and conclude that the tumor is the outcome of some change resulting in a new cell of fixed type.

In another way the results of transplantation have been misleading: they have masked the fact that the cells of most tumors, with the exception of those due to embryonic mischances, are sick

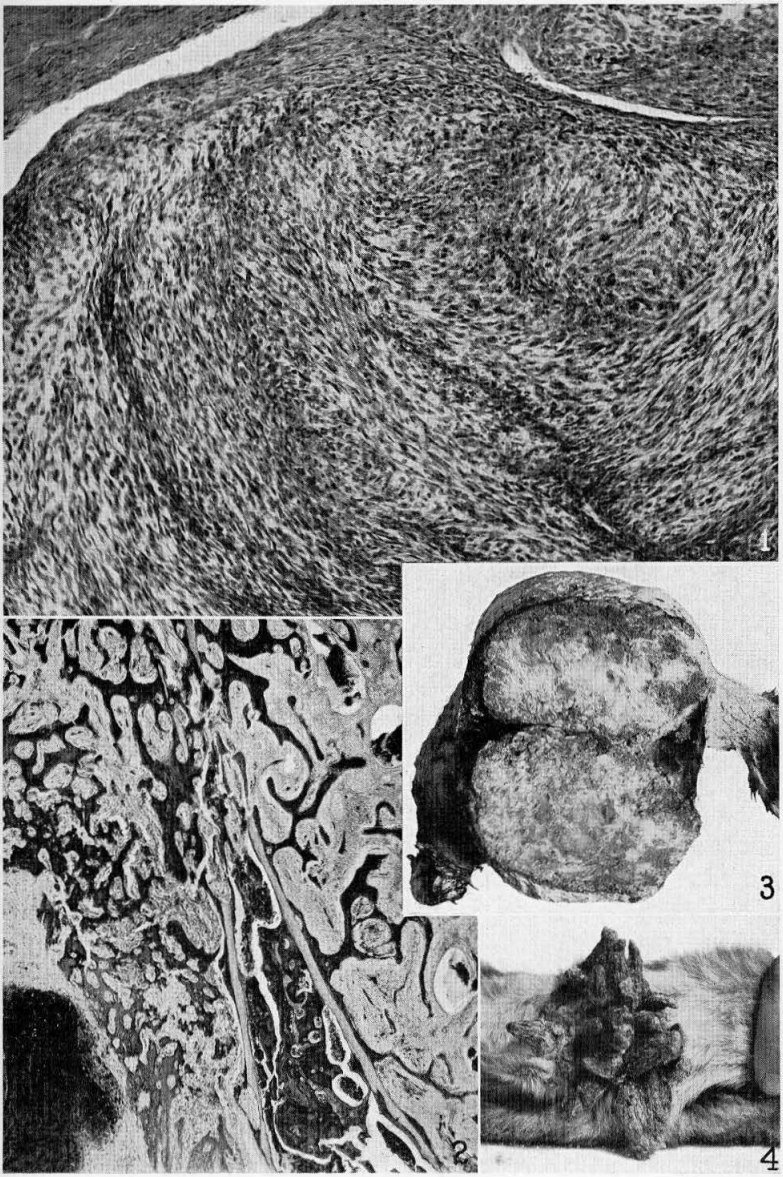
cells. It is no accident that the tissue of well-ordered, slow-growing tumors, chondromas or fibromas for example, will often flourish in new hosts, whereas that of many of the most malignant carcinomas and sarcomas fails to live. The shipper of oranges knows that many sorts of the fruit will not withstand transportation; that only the more resistant grades, not necessarily those most representative, will arrive in good state. It is much the same with the transplantation of tumors. Success depends not on what the original growth was actually like, but whether any of its cells can multiply under the new conditions. The opportunities are shuffled in such a way that those cells which are most hardy, usually the better-balanced ones, are the ones to persist and divide. In the course of a few transplantations all the maladjusted progeny of the original tumor may be left by the way. And so it comes about that sections of transplanted growths frequently offer a spurious impression of health. Acute morphological studies like those of Lewis (1) may be necessary to detect that the cells are sick. Yet as he remarks after studying successive transplants *in vitro,* "Tumor cells are notoriously afflicted with chromosome troubles"—though he deems the cytoplasmic changes of greater moment. In real tumors, meaning thereby spontaneous growths, the evidence of sickness is often outspoken. One can tell at a glance that the cells are upset. It is unnecessary to list the variety of abnormalities—multipolar mitoses, giant cells and giant nuclei, bird's-eye inclusions, keratohyaline lumps, etc.—which can be encountered in an ordinary squamous cell carcinoma, or to name the degenerative processes—mucous, colloid, fatty, hydropic, glycogenic—that tumor cells undergo as result, appar-

FIG. 1. Chicken sarcoma (Chicken Tumor I) resulting from the 7th successive transplantation of bits of the tumor tissue: metastasis in the gizzard.

FIG. 2. Osteochondrosarcoma of the fowl (Chicken Tumor VII). Section across the keel of the sternum, through the center of the spontaneous tumor. The keel can be seen in the midst of the growth, but its further end is lost in a mass of spongy bone.

FIG. 3. Osteochondrosarcoma (Chicken Tumor VII) caused by the injection into the upper leg muscles of a Berkefeld filtrate of a tumor extract. The growth has been cut across to show the intermingled cartilage and bone.

FIG. 4. Papillomas produced by rubbing the Shope virus into a scarified area on the skin of a domestic rabbit.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ently, of innate disturbances as distinguished from those due to faulty blood supply, pressure conditions and so forth. Some spontaneous tumors enlarge only because an immense mortality rate amongst their cells is exceeded by a greater rate of multiplication. Others grow because their cells divide before they can die. The cells of others appear "healthy" from first to last, but these are in general the growths due to developmental errors.

It might be expected, since tumor cells are in most cases sick cells, that they would tend to fall away from normal standards of organization. Certainly this is what happens. Sometimes they function excessively, melanoma cells for example forming pigment in amazing quantity. Tumors of the ductless glands have even served the organism in rare cases, when the gland itself was defective or had been removed; but comprehensive studies have shown that this functioning was fortuitous. Sometimes the cells undergo metaplasia, forming bone or cartilage (2) or myxomatous tissue perhaps, as result of a stimulation of their latent talents. But this is no unique phenomenon. It follows upon many sorts of pathological stimulation that have nothing to do with neoplastic growth. Rider's bone is a good example. The new tissue formed in tumors, whatever its sort, tends to be ill-arranged, and it is evidently purposeless. Amidst the immense diversity of the human tumors no organ of a new sort has been discovered. Many growths, however, make what might almost be termed pathetic efforts to maintain the normal standard of organization. The cells of a squamous cell carcinoma keratinize as well as their abnormalities permit, and often rapidly cover ulcerations that the growth itself has brought about; the cells of an adenoma may be grouped about a hypothetical duct. But as growth goes on morale is often lost, the process of organization is boggled worse and worse, and, within the period before the host succumbs, the proliferating tissue may have reached the final stage of degradation, a helter-skelter competition of its individual elements, with all efforts toward a useful functioning on their part completely given over. Before a tumor attains this condition, however, it may go through several phases each characteristic of the growth at that time; and its last state often has little resemblance to its first.

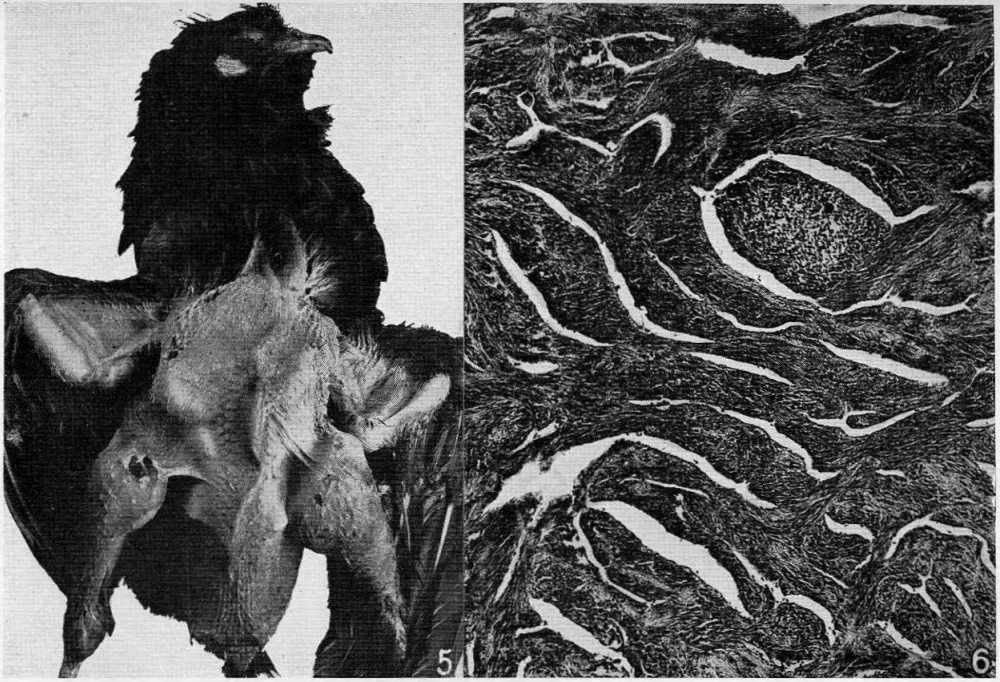


FIG. 5. Fissured sarcoma (Chicken Tumor XVIII) in a fowl of the second transplantation series. Tumor masses derived from the implanted material can be seen at either side of the sternum. There are metastases in both legs and one wing.

FIG. 6. Fissured sarcoma (Chicken Tumor XVIII). General character of the growths obtained, at an early period of propagation, by the transplantation of tumor tissue or the injection of a Berkefeld filtrate.

This is not an excursion in thought, but a recognition of the tumor problem as Nature presents it. Whatever the cause of tumors, it in most cases renders the cells manifestly sick and may bring about no little individual variation in them; it disturbs their organization and their special functioning, and it may do away with both. I come now to the evidence that viruses have just these effects and that some viruses cause neoplasms.

About 25 years ago chicken tumors were transplanted for the first time. This happened just after a renewed examination by scientists of the possibility that neoplasms in general might be due to parasites—an examination for which contemporary bacteriological knowledge and technics had provided the stimulus and the means. No parasite had been discovered but on the contrary numerous facts which seemed to indicate that tumor phenomena are due entirely to the neoplastic cells as such. The morphology and behavior of mammalian growths furnished strong support to this view, and the first transplantable chicken tumor studied with relation to its cause resembled these in its obvious characters. A spindle cell sarcoma (fig. 1), it was typically a neoplasm, even measuring up to the new criteria provided by experiment (3). Yet from its tissue something could be separated which caused similar growths when injected into healthy fowls (4), and further study showed that this held true of other chicken tumors, some of them organoid in character (5). The presence of causative agents distinct from the tumor cells could be demonstrated by differential filtration, or by drying or glycerination of the tissue, one method alone being successful in some cases, in others all three. The agents not only gave rise to tumors on introduction into normal fowls but to tumors with the characters of the original growth. One of the spontaneous tumors investigated was found on the sternum of a fowl (6). It was not enlarging, but looked like a symmetrical, benign, developmental anomaly, and it consisted mostly of cartilage and bony trabeculae extending out from the sternal plates (fig. 2). Yet transplantation was successful in a large proportion of hosts, the growth developing a sarcomatous element; and it yielded an agent causing the formation of precisely similar osteochondrosarcomas in other fowls, the stimulated con-

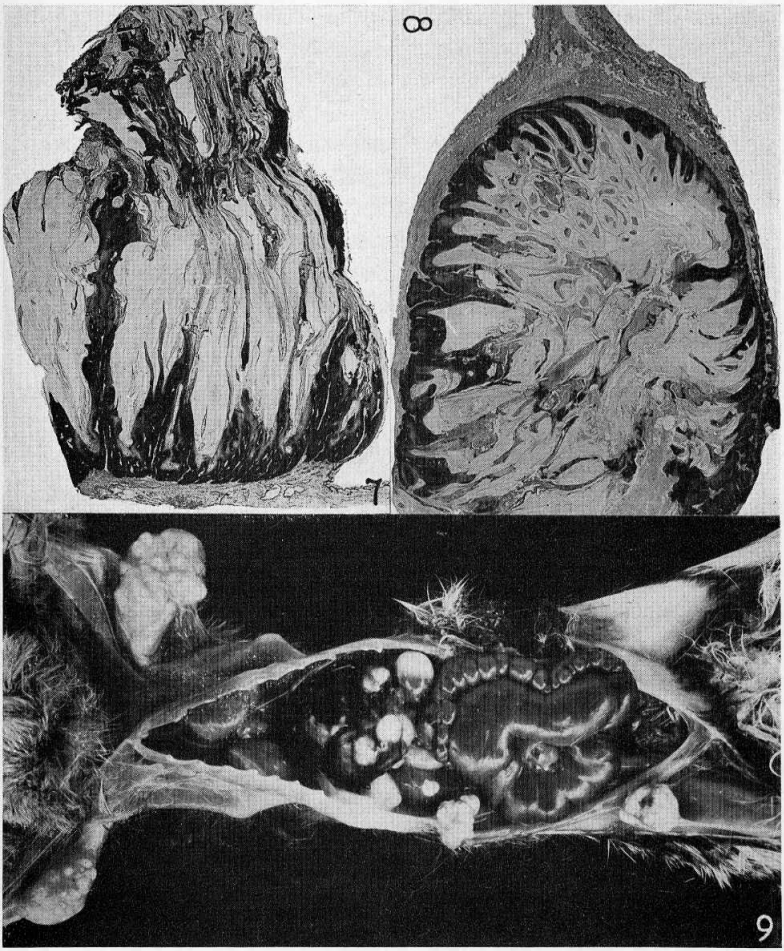


FIG. 7. Cross-section of one of the growths of fig. 4.

FIG. 8. Rabbit papilloma growing under skin which had been covered with collodion to prevent extension outward.

FIG. 9. Growths resulting from the experimental transfer of bits of the papilloma from the skin to the muscles of the forelegs, subcutaneous tissue of the groin, liver, kidney and spleen. The rabbit died on the 39th day after the implantations. The leg muscles and spleen had been almost entirely replaced. A large nodule was present in the healed abdominal wall.

nective tissue forming cartilage and bone by successive, metaplastic changes (fig. 3). In another instance (7) the primary tumor was in the gizzard and it had given rise to metastases in the voluntary muscles. It was a fibrosarcoma which tended to push into the blood vessels and enlarge there, still covered by endothelium, with result in an intracanalicular pattern (figs. 5 and 6). From this growth too a filterable agent was procured, which caused tumors of the same complex arrangement, with the same curious tendency to metastasize to the muscles. But just as happens with many spontaneous mammalian tumors this fowl tumor underwent a progressive degradation. The changes took place gradually, in the course of successive transplantations, the growth becoming a simple spindle cell sarcoma, much more malignant than before and with a morphology unlike that of the other spindle cell sarcoma under study in the laboratory at the same time (8).

Through the enterprise of many workers filtrable agents have now been demonstrated in a variety of chicken tumors—myxomas, fibromas, spindle cell sarcomas, a chondroma, an osteoma, a round-cell sarcoma and an endothelioma (9). Agents causing several forms of leukosis were recognized (10) even before the first sarcoma came to hand, and some of these, though causing leukemia when introduced into the blood stream, have given rise to tumors of sarcomatous or endotheliomatous type when injected locally (11). Epithelial growths are very frequent in fowls, carcinomas in special, but they have received little attention, owing to technical difficulties of transplantation. It is known only that they can be transplanted.

The presence of causative agents in the chicken tumors was more than a surprise; it seemed superfluous. Renewed experimentation with mammalian growths did not disclose the presence of any such agents. Hence the neoplastic character of the growths in fowls was doubted for a while, and for a further while some workers assumed that the so-called agents were actually fragments of cells, resistant to drying, so small that they would pass through filters, yet capable by proliferation of causing the same growths once again. These explanations proved untenable and resort to others became necessary. Whatever form they took, there was

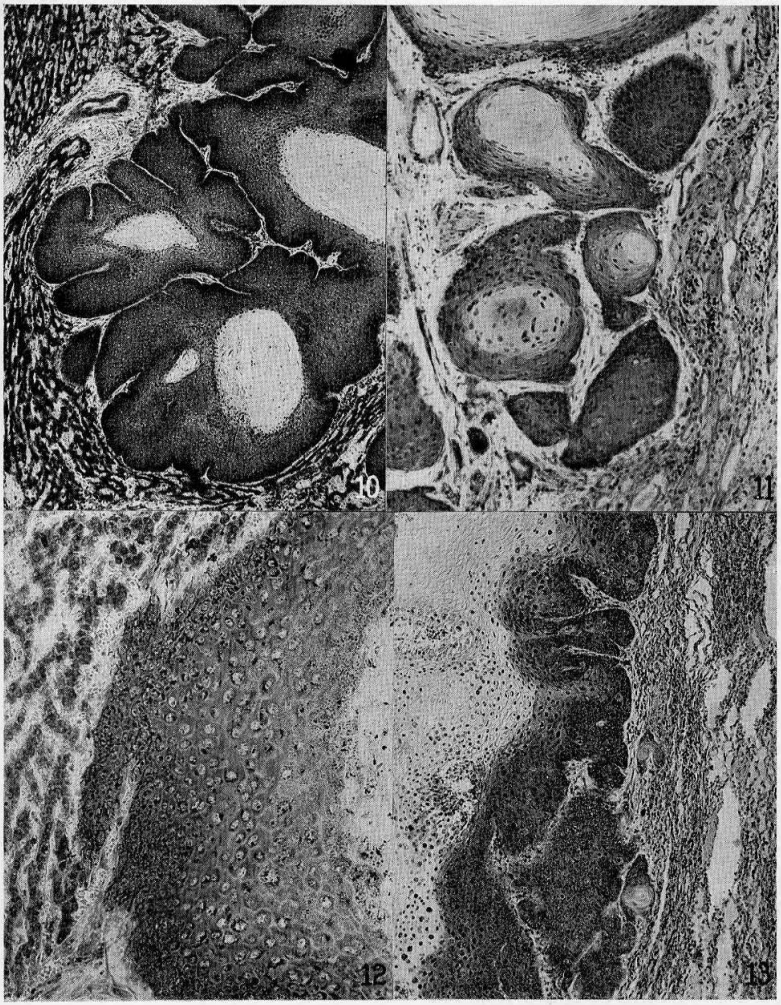


FIG. 10. Papilloma growing in the liver as result of experimental implantation.

FIG. 11. Margin of a papilloma growing in the kidney as result of implantation.

FIG. 12. Pigmented implantation nodule in the liver: to show the direct replacement of the parenchymal cords by the papilloma.

FIG. 13. Papilloma replacing the spleen after implantation. As in the other instances figured, the invasive growth is entirely unencapsulated.

one course obviously to pursue, namely to find out as much as possible about the tumor-producing agents. As a result of intensive studies many of their attributes and relations to the tumor and to the host fowl have been ascertained.

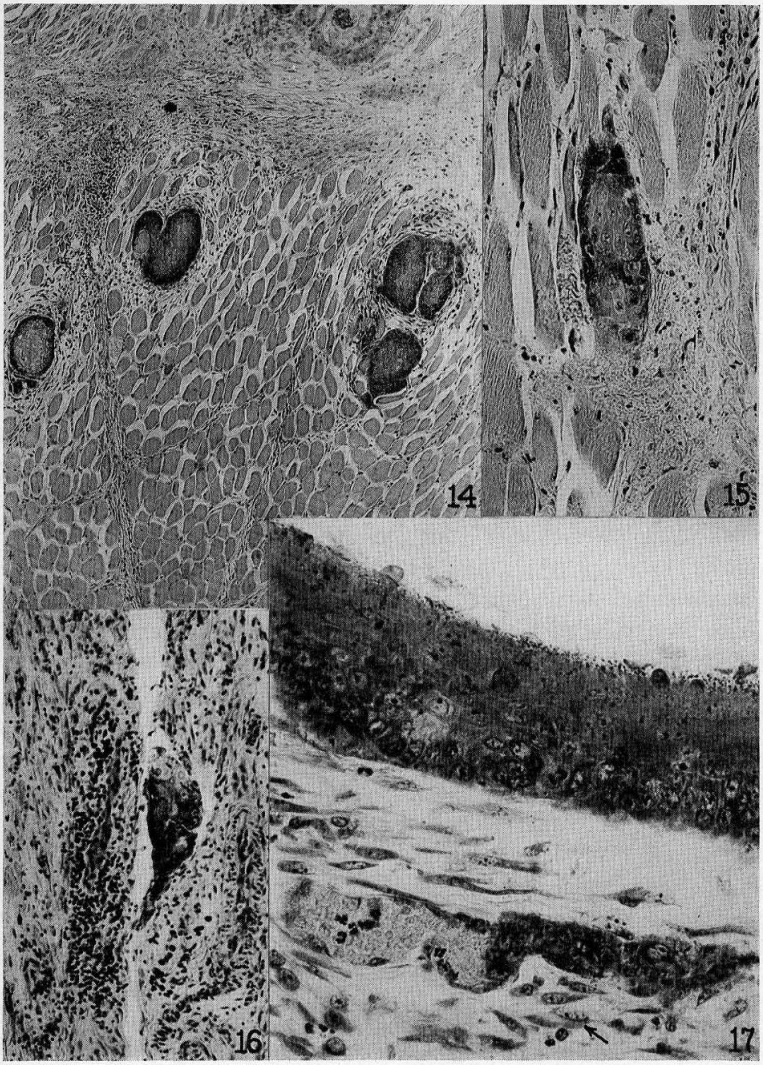
Each tumor-producing agent gives rise to a growth of a type characteristic of it, through its influence on cells of one kind. It seems able to affect only cells that have been injured, causing these to multiply with more or less derangement and to behave in abnormal, aggressive ways. None of the agents elicits any distinctive histological reaction other than the neoplastic proliferation: their activities find expression through the cells that do their bidding. Yet they have what might be termed a clandestine relationship with their hosts, for the latter frequently elaborate antibodies against them, which circulate in the blood and are capable of neutralizing them when they are in the free state *in vitro*, as when they have been procured in tumor extracts (12). But in the tumor itself the agents are not free. There they are intimately associated with the proliferating cells, and they continue to act upon these cells in spite of the antibodies (13), and the tumor continues to grow and the quantity of the agent to increase. Yet the antibodies do have one important effect: They serve to minimize or prevent reinfection with the virus, notably contact infection of the cells adjoining the growth. For this reason, and because the agent can act only upon injured cells, and because of other conditions not well understood yet obviously effective, the tumor grows by multiplication of the cells first influenced, it grows "aus sich heraus," in Ribbert's phrase. All of the obvious phenomena, those of morphology, of enlargement, extension, infiltration, metastasis formation, retrogression, the resistance sometimes manifested to further growth, even the

FIG. 14. Margin of a growth resulting from implantation of the papilloma in the leg muscles. There is a cellulitis due to bacterial infection. The proliferating epithelium is destroying and replacing the muscle fibers.

FIG. 15. Another specimen of the same sort: to show direct invasion and replacement of a fiber by the proliferating epithelium of the papilloma.

FIG. 16. Papilloma within a lymphatic.

FIG. 17. Margin of a growth resulting from an accidental implantation of the papilloma on the parietal peritoneum: to show direct invasion of a blood vessel by the epithelial cells (arrow).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happenings when the tumor is transplanted to favorable and unfavorable hosts, are referable to the neoplastic cells as such. Seeing what these do and the responses they elicit, one finds no need to look outside them for an actuating cause; their behavior appears to be the result of intrinsic disturbance. Yet a god exists in the machine, an agent which drives the cells on, which is separable from them, and can be kept for years in the dry state.

While all this was in process of discovery facts about viruses were accumulating from many directions, new viruses were being discovered, and new potentialities that they possess. It began to be generally recognized that some viruses may act to cause proliferation instead of necrosis, as long ago perceived by Borrel (14). Philibert (15), Rivers (16), and Andrewes (17) have each ranged viruses in a graded series according to their pathological effects, with those that kill cells forthwith at one end of the series and those that cause them to proliferate at the other. The most comprehensive series, devised by Andrewes, ranges from the frankly necrotizing foot and mouth disease and canary pox, through sheep pox and infectious myxoma to the infective warts—growths which have the morphology of tumors—and to a recently discovered virus disease of rabbits in which fibromatous masses are formed—the infectious fibroma of Shope (18).

Table 1 compares the activities and attributes of the chicken tumor agents and the viruses. It makes plain that the agents must be termed viruses or else that the criteria must be rejected whereby the latter are now recognized as such. The present uncertainty of what viruses actually are stands outside the dilemma. We need not ask ourselves whether they are alive or dead, chemical substances or organisms. It is enough for present purposes that they have certain distinguishing attributes, that they produce disease, and that this disease, naturally as well as experimentally, is transmitted by them.

Andrewes placed the chicken tumor agents at the further end of his series, amongst the viruses which cause proliferative growths. The most carefully studied of such agents would appear to rank with the larger viruses, measuring about 100 Mμ (19). Specific serum antibodies against it have been elicited by the repeated

TABLE 1

A comparison of the activities and attributes of the chicken tumor agents and the viruses

THE CHICKEN TUMOR AGENTS	THE VIRUSES
Both cause characteristic diseases by inducing morbid changes in cells. The cell changes are often distinctive of the causative entity but not always.	
The agents cause cells to proliferate and form more or less organoid, neoplastic growths.	The viruses cause cells to die, or to proliferate and die, or to proliferate in series with result in growths having the appearance of tumors, sometimes organoid (common warts, Shope rabbit fibroma).
The disease incidence does not suggest an infection.	So too with herpes virus, submaxillary gland virus.
Not contagious, inoculable only.	So too with many viruses.
Pathogenic for a single species or its close relatives.	So too with many viruses.
Effective only after tissue injury.[1]	So too with many viruses.
The agents sometimes lie latent.	So too with the viruses of herpes febrilis, of common warts, of lymphocytic choriomeningitis (Traub).
Both induce neutralizing antibodies with group and specific affinities, yet are protected by the cells.	
Invisible; filtrable; negatively charged; dependent for increase upon association with living cells.	
Adaptable—within limits.	
Varying widely in resistance to physical and chemical agencies, but without distinctive general differences in this relation.[2]	
Readily adsorbed and eluted; precipitated by slight changes in reaction; capable of some purification.	
Size about 100 Mμ (Chicken Tumor I).	So too with medium-sized viruses.
Agent of Ch. T. I is thrown down by centrifugation at speeds which throw down many viruses.	

[1] Youth does not render cells susceptible. The mesoderm of inoculated embryos is affected by the agent only where injured (Ch. T. I).

[2] The evidence for a distinctive resistance of the agents to ultraviolet light is now deemed equivocal by its discoverer (Baker S. L.: Brit. J. Exp. Path., *16*, 148, 1935).

injection of the tumor tissue into insusceptible animals of other species (20). The agent has been thrown down with the centrifuge, and elements presumably representing it have been disclosed by stains (21). But the possibility of adsorption upon organic matter and the dot-like character of the stained elements render interpretation of these findings difficult.

Are mammalian tumors also due to viruses—some of them at least? This prime question remains, and recently a material has come to hand wherewith it can be studied. A virus-induced papilloma is now available for experiment which possesses the immediate attributes of a tumor and not infrequently becomes a genuine cancer.

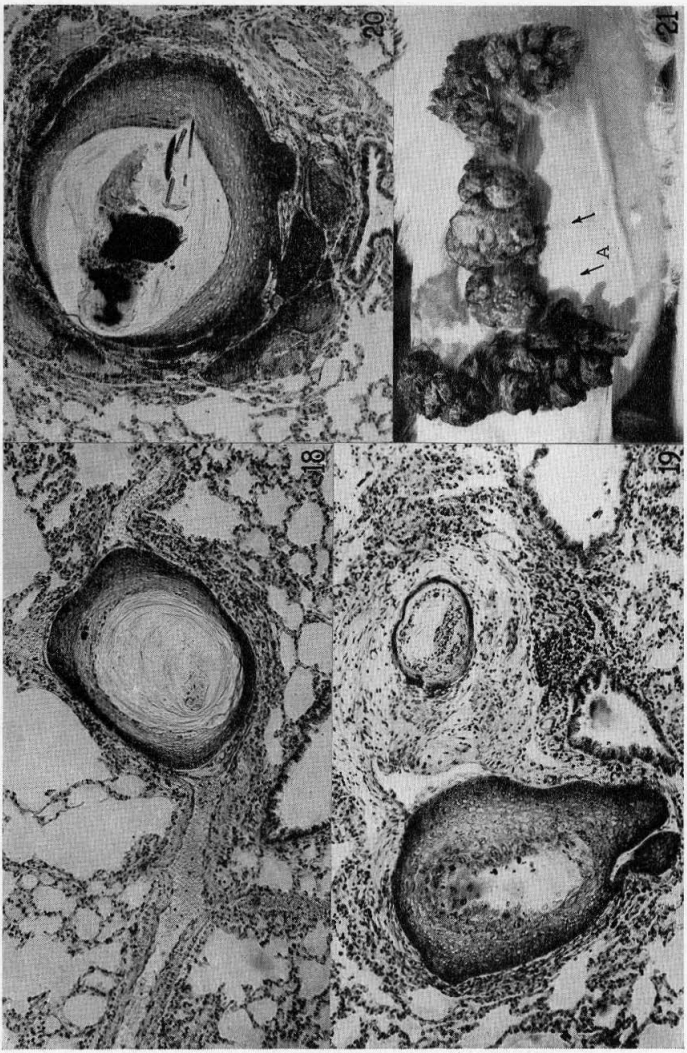
Hunters in Kansas, Iowa and Texas often find large warty masses, or cutaneous horns, on cottontail rabbits. Several years ago Doctor R. E. Shope, of the Princeton branch of the Rockefeller Institute, proved that these growths are due to a virus, so small that it passes even through Chamberland filters, capable of withstanding temperatures up to 65°C. for 30 minutes, and enduring long in active form outside of the body (22). To produce growths one has only to rub the virus-containing material into the scratched skin of a normal rabbit. Shortly a red roughening appears, then close-crowded papillae, and these rise and enlarge to form high peaks that dry on the top after a time (fig. 4). The growth is an orderly, superficial papilloma (fig. 7), as Hurst showed, often like an immense wart or again like a horn.

Verruca vulgaris of man is due to a virus (23) and so too are the infectious papillomas of dogs (24) and cattle (25). These do

FIGS. 18 AND 19. Survival and growth in the lung of emboli of papillomatous tissue. The rabbit was killed 5 days after intravenous injection of bits of a papilloma induced on its skin by virus inoculation. Fig. 18 depicts an enlarging embolus at the fork of a vessel; fig. 19 another such embolus from which epithelial cells are extending into the pulmonary tissue, as also an embolus that is dying.

FIG. 20. A further stage of the growth in the lung of emboli of papillomatous tissue. Invasion of the lung is actively under way, but the position of the material originally injected can be told by the included fragments of hair.

FIG. 21. Fungoid carcinomas that have replaced two virus-induced rabbit papillomas. Arrows point to the growths. A slice was taken from the one designated as *A*. Fig. 26 shows the edge of this slice. It is a malignant papilloma.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not grow indefinitely, but have a habit of going as rapidly as they come, and daughter growths or satellite growths are fairly frequent in the individuals affected. The rabbit papilloma has significantly different characters. When caused by active virus in favorable hosts it tends to enlarge progressively; and it does not seed itself to other spots on the skin, with growths appearing there secondarily. Often the papillomas induced in domestic rabbits enlarge with special rapidity, forming great masses of proliferating tissue; yet from this tissue, which one would expect to yield an especially active virus, none can be recovered by the technical means which yield it in abundance from the papillomas of cottontails. This negative result recalls the failure to demonstrate causative agents in mammalian tumors generally, as Shope pointed out.

The realization of these facts led to experiments (26) to find out how far the papilloma resembles a true tumor; for there seemed to be some possibility that it could be utilized as a stalking horse for the tumor problem. Experiments were made possible by repeated generous gifts of virus material from Doctor Shope; and Doctor J. W. Beard and, more recently, Doctor John G. Kidd have participated in the work. Both the natural hosts of the virus—cottontail rabbits—and domestic rabbits have been employed.

The virus causes disease only in rabbits and is effective only where brought in contact with damaged cells, the initial proliferation being strictly limited to the large or small areas of traumatized epidermis into which it is introduced. Where a needle carrying the virus has been thrust into the skin, there a punctate growth arises, which steadily enlarges in hosts that are favorable. The cells in the lower layers of the epidermis multiply and extend downward to the barrier of the fibrous corium, after which the growth takes the way of least resistance and projects outwards. Enlargement appears to be wholly by intrinsic cell multiplication, and it is actually so, as experiment has shown. Though possessed of notable proliferative power, the papilloma for a long while has little aggressiveness; yet if covered with collodion at an early stage it will grow downwards (fig. 8), and it often takes advantage of any disturbance in the underlying connective tissue, pushing

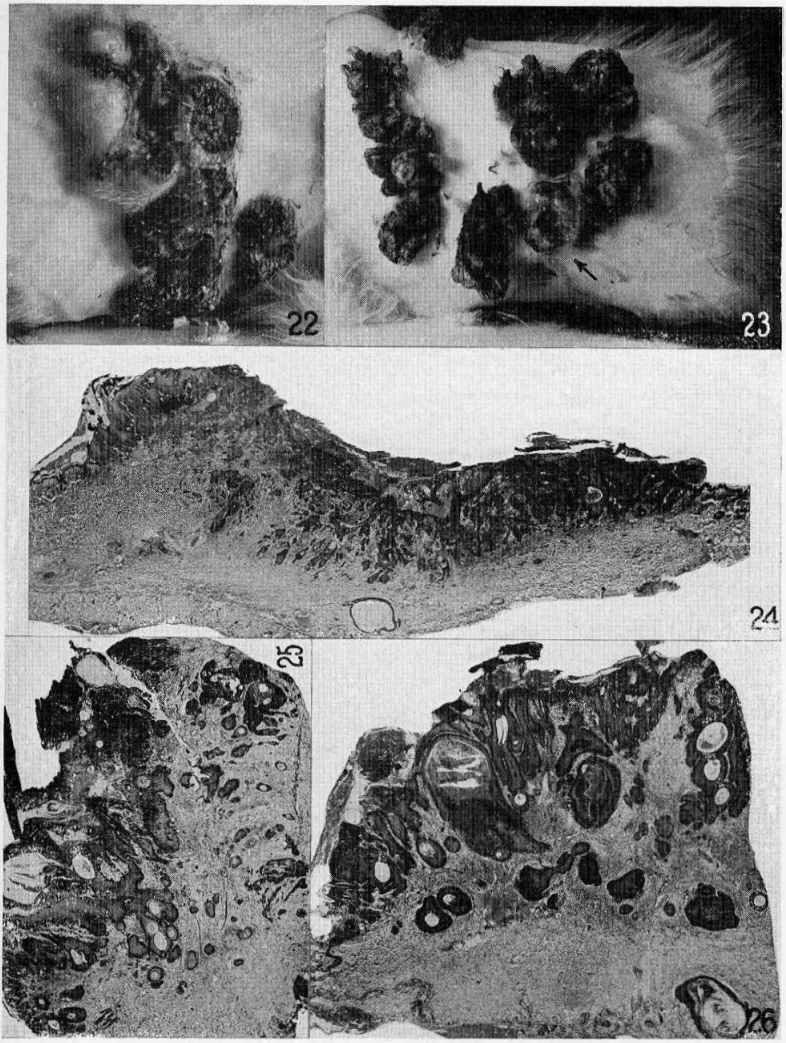


FIG. 22. Ulcerating cancer that has replaced one papillomatous mass and is encroaching on another.

FIG. 23. Ulcerated cancer that has replaced one papilloma (arrow) of the several that are present.

FIG. 24. Cross-section of the cancer of fig. 23. It is a squamous cell carcinoma.

FIG. 25. Section through the edge of the cancer shown in fig. 22. It is a malignant papilloma, breaking up into squamous cell carcinoma as it extends downward.

FIG. 26. Section showing the edge of a slice taken from the papilloma in fig. 21.

deeper where this is inflamed. When the living papillomatous tissue is shaved off and implanted in the subcutaneous tissue, voluntary muscles and viscera of the host, it becomes vascularized and behaves in a way that proves the skin to be a relatively poor situation for it (figs. 9–13). Nevertheless, epidermal cells are the only ones on which the virus will "take," not even the mucous membrane of the cheek proving susceptible, much less that of the rectum, esophagus or the epithelium of the lungs. The growths that develop in the inner organs are the results of a genuine transplantation. The surviving cells proliferate rapidly, often invade and destroy, and form large masses which frequently lead to death. In these the papillomatous arrangement is ordinarily manifest, though when their growth is attended by connective tissue proliferation, due to bacteria lugged in with the implanted tissue, the aspect may change to that of a squamous cell carcinoma (figs. 14 and 15). Bits of the growth accidentally distributed in the abdominal cavity during implantation of the viscera find successful lodgement on the peritoneal lining—as do only the more malignant mouse and rat tumors under similar circumstances—and give rise to multiple growths. Recurrence after excision is frequent. The multiplying cells, both of visceral and skin growths, often penetrate into the lymph and blood vessels (figs. 16 and 17), and secondary nodules sometimes develop in the lungs after operation. Fragments of the papillomatous tissue, that have been purposely introduced into a vein to be carried to the lungs, frequently survive there, proliferate, become organized, and, penetrating the arterial wall, extend into the pulmonary tissue (figs. 18–20). The course of events is precisely the same as in the case of blood-borne emboli of human carcinomas when these give rise to lung metastases (27). Sometimes the papilloma retrogresses, especially when situated on the skin; and the changes occurring then are precisely like those taking place in and about the true epidermal tumors when retrogressing, notably the tumors induced by tarring.

It is evident that the papilloma has the immediate attributes whereby tumors are recognized to be such. Nevertheless one cannot think of the growth as a tumor of typical sort. For it is obviously infectious in nature and due to an easily demonstrable cause.

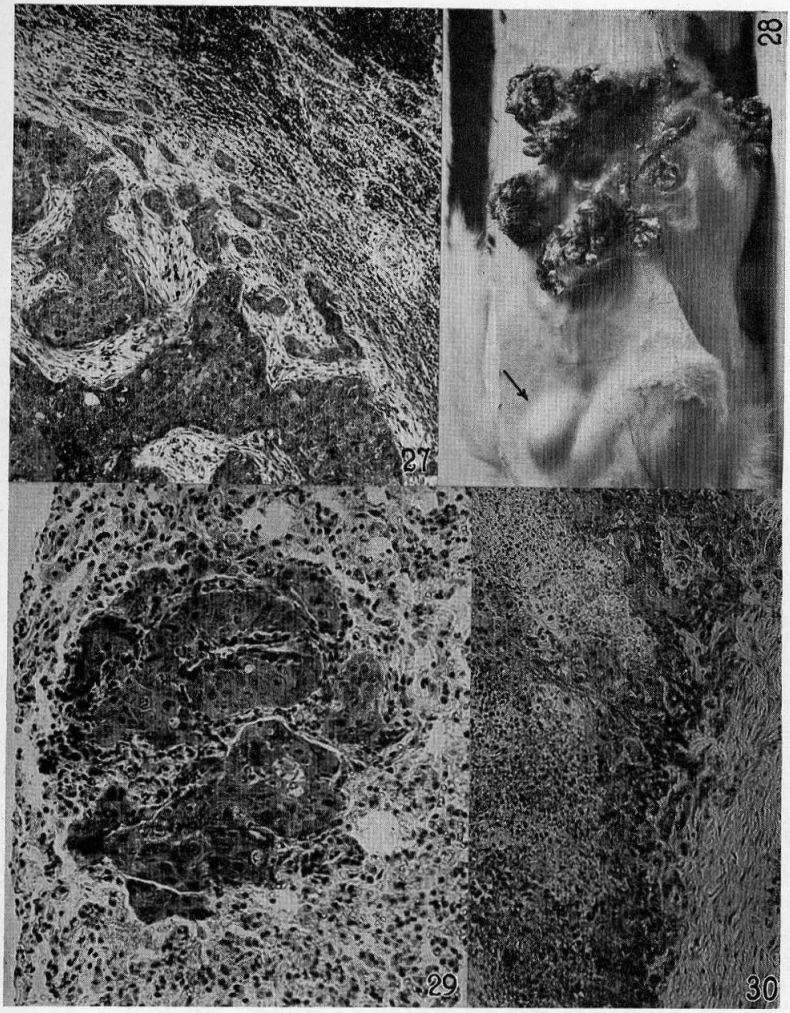


FIG. 27. Metastasis in an axillary lymph-node of the cancer shown in fig. 23.

FIG. 28. The cancer of fig. 23 after a further 78 days. It has undermined and destroyed several neighboring papillomas. Another axillary metastasis has appeared (arrow).

FIG. 29. Lung metastasis from a cancer arising in a virus-induced rabbit papilloma.

FIG. 30. Retroperitoneal metastasis of the cancer of fig. 23. The growth has extended from a lymph gland to the wall of the aorta and has become extremely anaplastic.

This is not true of ordinary tumors. Yet the experimental findings have made plain the fact that a virus can cause a mammalian growth with tumor characters and does actually cause one. It will be recalled that recognition of the neoplastic nature of the chicken tumors preceded the demonstration of their virus cause. In the case of the papilloma events have taken the opposite direction—a growth due to a virus has been shown to have the characters of a neoplasm. The trails have met at the same lookout. What does one see from this?

One sees first and clearly that the viruses responsible for the chicken tumors and the rabbit papilloma have similar biological effects, speaking by and large. Both cause and direct distinctive neoplastic growths while themselves remaining hidden; and the same working conditions obtain for both. Both act only upon injured cells, urging these to tumor formation. The Shope virus, like the chicken tumor viruses, elicits neutralizing antibodies which circulate in the blood of the host, and like them it remains effective because shielded by the infected cells (28). All the obvious tumor phenomena are referable to the activity of these cells. Yet when the virus is weak or experimentally attenuated, the growth lolls along and often retrogresses.

The fact has already been stressed that many mammalian tumors of undetermined cause fall away progressively from the organized state, their cells multiplying ever more rapidly, and becoming more and more malignant and anaplastic. The same

FIG. 31. Early extension of a papilloma into the fibrous corium (47 days after virus inoculation).

FIG. 32. Later irregularity and extension downward of a papilloma, with pearl formation (72 days after inoculation).

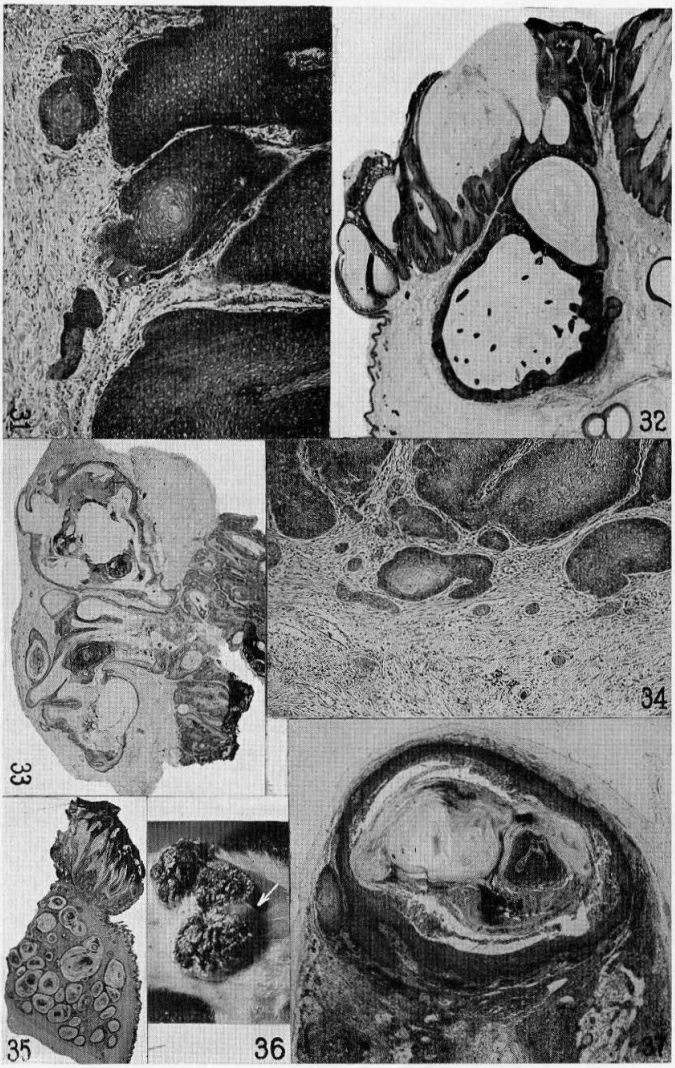
FIG. 33. Cystic, malignant (?) extension of a papilloma into the subcutaneous tissue.

FIG. 34. Squamous cell carcinoma deriving directly from the base of a papilloma.

FIG. 35. Invasive, cystic growth deriving from a papilloma. It has extended far out under the neighboring skin.

FIG. 36. Precancerous stage of the papillomatosis. The high peaks have been replaced by flaky material and the base of the growth is fleshy, with a raised, tense margin. A large subepidermal pearl has recently appeared outside the latter (arrow).

FIG. 37. Metastasis of a malignant papilloma in a lymph-node. The cystic nodule contains keratinized material which is papillomatous in arrangement, as is also the living epithelium near its center.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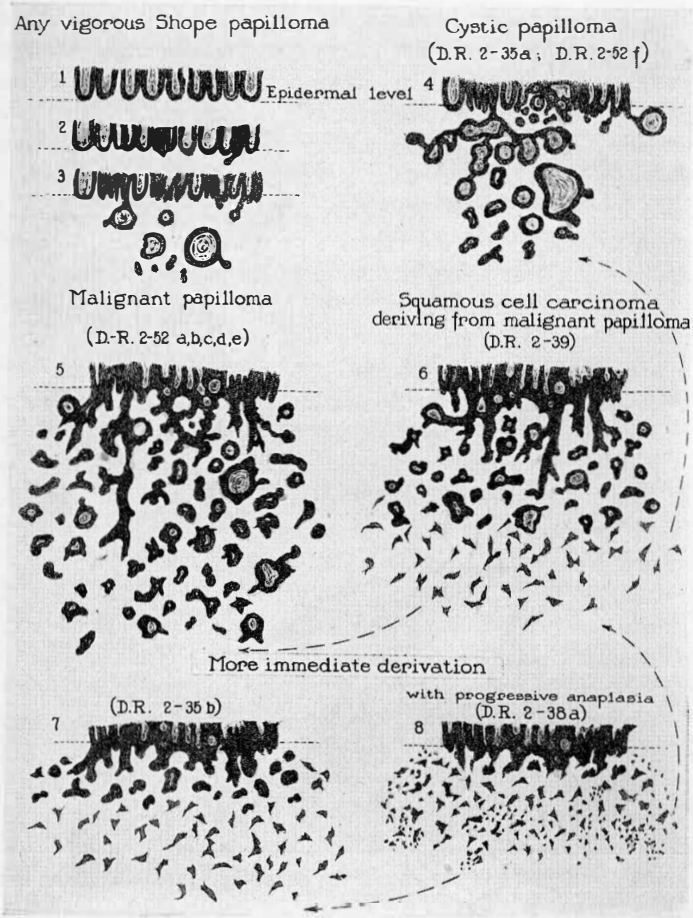
tendency has been noted of some chicken tumors due to viruses, as for example the intracanalicular sarcoma which became an ordinary spindle cell sarcoma. Recently some of the virus-induced rabbit papillomas have been observed to undergo changes of even broader scope, many of them altering from wholly benign tumors to very destructive cancers (29). With this occurrence the study of the Shope papilloma has lost its academic character; for the cancers have all the reality of those found in man. Many have now been studied, but it will suffice to report here on those developing in the first group of animals in which malignancy appeared. Ten domestic rabbits with especially vigorous papillomas were maintained, to learn the eventual fate of the growths. In eight of the animals cancer appeared after 4 to 7 months. The ninth rabbit died early in the cancer period, and the papillomas of the tenth retrogressed during it. Often the cancers were multiple. In one animal killed before malignancy was advanced sagittal sections disclosed 22 separate cancers in 13 of the 19 discrete papillomas that were present, and the other 6 growths were in a precancerous state. All of the tumors (figs. 21 to 30) have been cystic or fungating malignant papillomas, or ulcerative and far more malignant squamous cell carcinomas, or else representative of some stage transitional to these last. In six of the animals metastases developed, to the lungs alone in one case, to lungs and lymph nodes in another and to the nodes alone in the remaining four. The cancers killed 6 animals, the others dying of intercurrent causes. Two of the tumors were successfully transplanted to new hosts.

Significant changes take place in the papilloma before cancer appears. Mention has been made of the fact that when it is growing on the skin, its natural habitat, it often thrusts down processes into the corium (fig. 31). Here as time passes scar tissue forms, owing to repeated trauma and bacterial infection of the projecting growth. As months pass the scar tissue becomes disorderly, and in proportion as it does so the papilloma penetrates, often forming deep cysts or pearls (figs. 32 and 36). Growths in which this happens are the ones that become cancerous; and to tell precisely when malignancy supervenes has not been possible (figs. 33 to 35).



TEXT-FIG. 1. The progression to carcinoma: schematic drawing. The numbers in brackets refer to rabbits in which tumors illustrative of one stage or another of the progression were encountered; and the added letters designate the individual tumors of each animal. Many growths underwent further changes after they had become malignant, a fact indicated by the arrows.

The cancers originate from the cells affected by the virus, and only from them. This is clear not alone from their mode of development but from their histological character which is that of

growths arising solely from the epidermis, never from the skin appendages. They are pure-line epidermal tumors. The course of events can be shown diagrammatically. Text-fig. 1 is based on a study of more than 70 instances of malignant change, with successive biopsies in many cases. The change from benign papillomatosis to carcinomatosis occurring in the rabbits is like that not infrequently witnessed in human tumors, notably in oral, laryngeal, bladder and intestinal papillomas, and in papillomas of the skin, including the tar and paraffin papillomas.

What causes the rabbit cancers? In accounting for them it is well to set aside for the time being the fact that they arise in tissue stimulated to neoplastic growth by a virus, for this fact may be quite immaterial. One should try to explain the cancers in terms of the hypotheses that seem most reasonable nowadays, just as one would explain other tumors. Many people hold that tumors result from mutations occurring in somatic cells, and others believe that they are due to substances produced by the cells and capable of causing others not only to become neoplastic but to form the same substance again. As a corollary to the latter idea, vague but hopeful mention is made of the substances discovered by Spemann, which are formed in embryonic tissue and influence its differentiation in one way or another, so that teeth, for example, may be formed in a salamander's mouth that would ordinarily remain toothless.

On scrutinizing the course of events in human or rabbit papillomas (text-fig. 1) which go on to cancer one sees that a formation of

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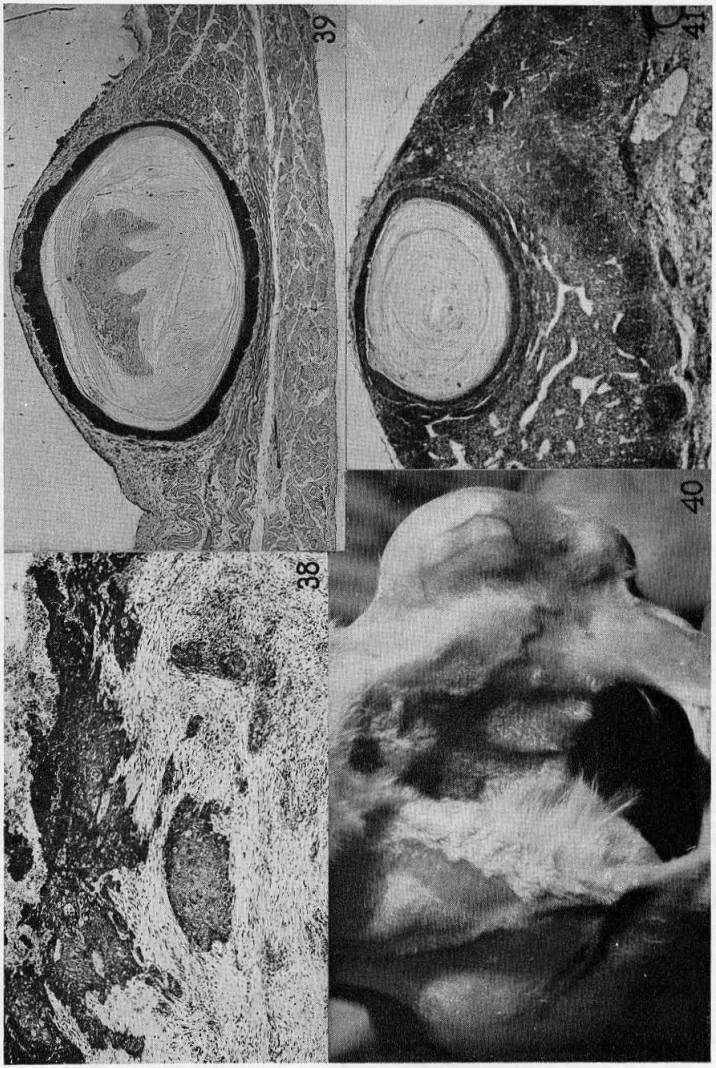
FIG. 38. Section of one of the growths shown in fig. 40. It is a squamous cell carcinoma.

FIG. 39. Implantation nodule resulting from the intraperitoneal injection of bits of tissue procured from a skin papilloma 2 days after it appeared. The rabbit was killed 26 days later. Fig. 17 shows part of the cyst wall, and the invasion of a blood-vessel.

FIG. 40. Growths in the forelegs of a rabbit to which a cancer deriving from a papilloma had been transplanted.

FIG. 41. Two metastases in a regional lymph-node from a cystic, malignant papilloma such as is shown in fig. 35. One is only partially shown, at a lower corner of the figure. The growths are cystic, their interior being filled with concentric layers of keratinized material like that in the implantation nodule of fig. 39. Their cells appeared less invasive than did those of the latter, which had extended into a blood-vessel (fig. 17). Compare also with the cysts of fig. 32.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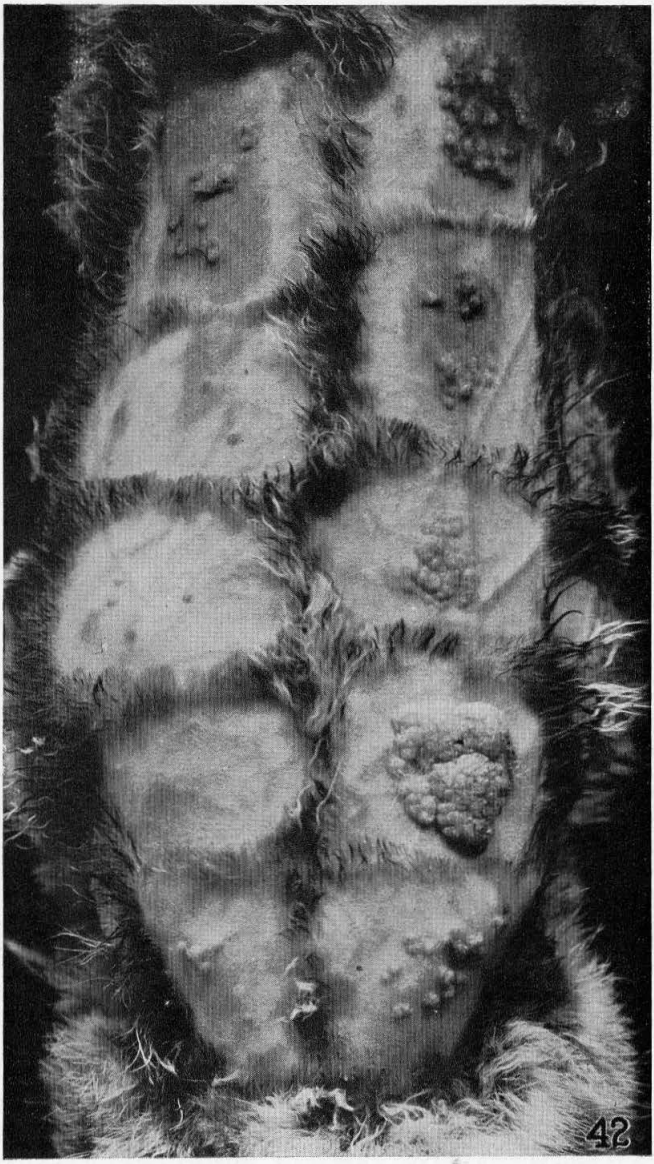
organizing substances will not account for the phenomenon. Organizers build up; here all is pulled down. Nor will a single disorganizer or other autogenous chemical entity fit the case. Many of these unique and hypothetical substances would have to be produced in succession to account for tumors which assume one form and character after another while on their way to anaplastic malignancy, tumors which often remain at this stage or result in a growth characteristic of the stage.

The way in which the papillomas change to cancers would seem, at first thought, to favor the mutation hypothesis. Though the malignancy appears to result from a progressive transformation of the cells, it involves more than an intensified activity of the papilloma. For many months the latter retains its essential character, though becoming disorderly, and then in the course of a few days or weeks it often changes to a squamous cell carcinoma. In other instances the alterations are so slight that one may be left uncertain whether cancer is actually present until metastasis formation—which the unaided papilloma never quite accomplishes—makes this plain. Something fundamental has happened, something qualitative and in most instances irrevocable. One might suppose that a somatic mutation had taken place except for the character of the new tumor. For as the elder Haldane has pointed out (30) when rejecting the mutation hypothesis of tumor origin, "Even when a chromosomal mutation is inconsistent with the ultimate survival of the developing organism its growth is still coördinated." The growth of the rabbit cancers is uncoördinated. And one would have to suppose a series of mutations, each essentially unlike any mutation ever observed before, to account for the variety of the successive, neoplastic manifestations.

As just remarked, the change from ordinary papilloma to another tumor is sometimes so slight that there may be difficulty in telling if, or when, it has occurred It seems to be the expression

FIG. 42. Results of inoculating mixtures of Shope virus with sera of differing neutralizing power, obtained from rabbits carrying papillomas. On some of the skin squares no growths have appeared, attesting to complete neutralization, while on others there are discrete papillomas in large or small numbers. The control mixture with Tyrode solution has given rise to confluent papillomatosis.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of the slightest possible alteration in the agent responsible for the growth. And this agent is the virus. Can one suppose that the latter undergoes variation as conditions in the papilloma become more unusual, and that virus variants are responsible for the cancers? Let us examine this possibility in the light of the facts.

Many chronic irritants of diverse character give rise to cancer and amongst them not a few parasites, for example the tubercle bacillus of lupus lesions in which carcinoma arises, the Bilharzia ova which cause bladder papillomas that become cancerous, and so on. Has the virus a nearer relationship to malignancy than these living irritants whose rôle is ended once the cancer has begun? True, the primary lesion that the virus causes, namely the papilloma, is neoplastic in character. But this may merely make the case more complicated, not necessarily different.

The fact is well attested that the more effective the virus, as evidenced by the behavior of the papilloma, the more likely is cancer to occur. It does not occur in retrogressing growths and it is rare in persisting ones that do poorly. But all this may mean no more than does the failure of cancer to occur when non-specific carcinogenic stimulation (x-raying or tarring, for example) is carried on for an insufficient period, or not vigorously enough. Cancer can be induced in cottontail rabbits by tarring the ears,[2] yet none of the virus papillomas in these animals, the natural hosts of the virus, has gone on to cancer, for the sufficient reason that in none has the growth had the sustained vigor it manifests in domestic rabbits.[3] Nearly all of the papillomas of cottontails eventually retrogress, and the few that persist remain circumscribed and are well tolerated. The relation between the virus and its natural host has approached a balance such as is so often observed when the relation between a parasite and the animal it affects has existed for a lengthy period. Under such circum-

[2] It has been caused thus in three instances in our laboratory, with pulmonary metastases in one of them.

[3] Since this was written Syverton and Berry (Proc. Soc. Exp. Biol. & Med., **33**, 399, 1935) have reported upon a cancer that originated in a naturally occurring papilloma of the cottontail. The instance must be regarded as highly exceptional.

stances the parasite tends to become a symbiont, as Theobald Smith has pointed out (31). In domestic rabbits the virus finds a fresh field, and is able to cause progressive, exuberant growths. One is reminded of the serious disease that ensues when *Trypanosoma gambiense* or *T. equiperdum* finds its way from the natural, wild host, which it scarcely troubles, to cattle and horses previously unexposed to attack. In domestic rabbits the Shope virus produces papillomatosis in its worst form and the outcome is cancer, however caused.

If one could get from the rabbit cancers a virus that caused other cancers forthwith this would be decisive. But it has not been possible even to procure from the preliminary papillomas the virus with which these growths were induced. All of the cancers have arisen in domestic rabbits inoculated with strains of virus which could not be recovered from the papillomatous tissue, as experiment had already shown. Nor has virus been recovered from the cancers.

These negative findings suggest the possibility that the virus may do no more than start the papillomas. As bearing upon the matter, a study has been made of the neutralizing power of the blood of domestic rabbits carrying growths induced with a carcinogenic virus strain (fig. 42). Such power was wholly absent from the serum until after the papillomas had begun to develop, and it appeared and increased in proportion as the growths enlarged (32). Evidently then the virus thrives in the papillomatous tissue. And recently Shope has obtained strains of it which can be readily recovered in active form from the papillomas induced therewith in domestic rabbits (33).

It should be possible to tell by the neutralization method whether the papilloma virus, or perhaps a variant upon it, is present in the cancers. One need only transplant such growths and test the serum of the new hosts to see whether it develops a neutralizing power for the virus. Two rabbits bearing transplanted cancers have recently become available for the test (34). One of these with large cancers yielded a serum of marked neutralizing power, while the serum of the other, with a small, recent nodule of the same implantation, neutralized slightly yet dis-

tinctly. The sera of two rabbits implanted ineffectually with the cancerous tissue and that of two normal controls of the same breed, kept under the same conditions, were devoid of significant effect on the virus, like the specimens from numerous normal domestic rabbits tested in other, different relations. An axillary metastasis had been utilized as material for the transplantations, thus effectually ruling out the possibility that papilloma cells had been accidentally transferred to the new hosts with the bits of cancer. The transplantation tumors, like the metastasis providing the material, were squamous cell carcinomas devoid of papillomatous characters (figs. 38 and 40).

The demonstration that the papilloma virus exists in the eventual cancers does not necessarily mean that it is their cause; for wholly extraneous viruses (vaccinia, and virus III, for example), when experimentally introduced into tumors, find safe harbor there (35), persisting long after the blood has developed neutralizing power and the animal itself has become immune to reinoculation. The Shope virus was inevitably introduced into the cancers as they developed from the papillomas. One must look for other evidence that it had any share in the malignancy. Some such evidence is at hand.

The existence of the virus in the cancers is attested in many instances by the morphological character of the growths, and so too is its formative influence upon them (36). The virus stimulates the epidermal cells to certain peculiar activities out of the many of which they are capable, as dermatological textbooks show. The result is the papilloma. Some indications that the virus is still influential in the cancers are provided by those malignant tumors which still exhibit the papillomatous morphology (fig. 26). The cancerous cells often form cysts in the same way as do the papilloma cells. In one instance a cyst secondary to a cystic cancer developed in a groin gland. Its individual cells were malignant yet it resembled the cysts formed by the ordinary papilloma under experimental conditions (figs. 39 and 41). In another instance a gland metastasis, more obviously malignant, had retained the papillomatous structure (fig. 37). Many of the cancers are but slight distortions of the papilloma, invasive and

TABLE 2

The antiviral serum titre of rabbits with transplanted cancers

DAYS	RABBITS	5 PER CENT VIRUS 0.5 cc. + 0.2 cc. serum + 0.3 cc. Tyrode						1 PER CENT VIRUS 0.5 cc. + 0.5 cc. serum							1/10 PER CENT VIRUS 0.5 cc. + 0.5 cc. serum						
		LT	ST	N1	N2	C1	C2	LT	ST	N1	N2	C1	C2	Tyr.	L	S	N1	N2	C1	C2	Tyr.
16	1	0	+−	0	+++	+−	0														
	2	0	0	+++	++	+++	+++−														
	3	0	+	+++	++++	+++	+++														
	4	0	++++	?	++	+++++	++														
20	1							0	0	++	++	++	+++	+++							
	2							0	0	++++	++	++++	+++	0							
	3							0	0	+++	+++	++++	++++	++							
	4							0	0	+++	+++	+++	++	++							
27	1														0	0	+	0	++−	0	0
	2														0	0	+	+	++−	++−	+
	3														0	0	+	+	++−	++−	+−
	4														0	+−	++−	++−	++−	++−	+−
34	1	+−	+++	+++−	++++	++++−	+++−	0	+	+++	+++−	+++−	++	++	0	0	++−	+−	++−	+−	0
	2	++	++++	++++	++++	++++	++++	+−	++−	++++	++++−	++++	++++	+++−	0	+−	++−	++	+++−	+−	++−
	3	+++	++++	++++	++++	++++	++++	+−	++−	++++	++++	++++	++++	+++	0	0	++	++	++	+++−	+
	4	++−	++++−	++++	++++	++++	++++−	+−	+−	+++	++++−	++++	++	++	0	+−	++−	++−	++−	++	+

LT, large tumors; ST, 1 small tumor; N, implanted, but no tumors; C, normal control; Tyr., Tyrode control

growing downward instead of folding outward. Only when the tumor has reached the stage of anaplastic squamous cell carcinomatosis, that is to say when its cells are no longer capable of the structural association and peculiar pathological differentiation characteristic of the papilloma, is the influence of the virus no longer manifest.

The behavior of the papilloma while it is still merely such indicates that it has some malignant potentialities. Recognition of these led indeed to the maintenance of the original group of animals in which cancer developed. Figs. 8 to 17 and 31 and 32 depict burrowing, enterprising papillomas, their penetration into blood and lymph vessels, and the destructive growth which may take place after implantation in the organs. The undisturbed papillomas of several cottontails penetrated deep into the subcutaneous tissue, and in one animal the cells grew along the lymphatics to the nearest gland, which they completely replaced (figs. 43 and 44). The lymphatic extensions were like those recorded for cancers of the human breast by Handley (37)—save in that they rounded out secondarily into cysts—yet the growth retained the morphology of an ordinary virus-induced papilloma and now, after the lapse of 21 months, it has almost completely disappeared. An indubitable cystic cancer, derived from a papilloma, extended along the lymphatics in the same way (figs. 45 and 46).

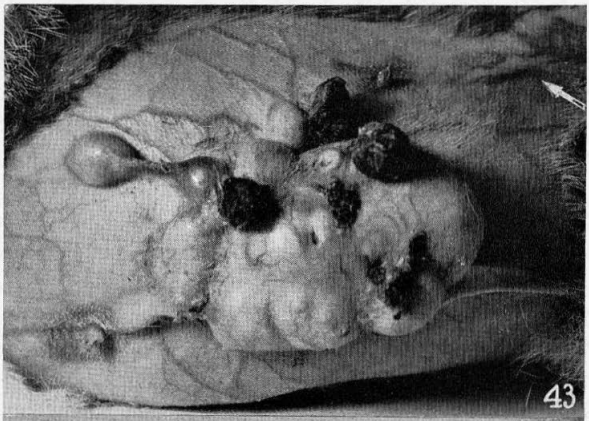
The behavior of papillomas that go on to cancer is indicative of gradually increasing capabilities; but even at an early period favorable conditions will cause them to invade and destroy, as has already been remarked. Trauma, bacterial infection and connective tissue inflammation exert a favoring, stimulating effect on skin papillomas, which becomes pronounced as time passes.

FIG. 43. Subcutaneous extensions from virus-induced papillomas in a wild rabbit. A lymph gland had been reached and totally replaced at the spot to which the arrow points. A healed biopsy wound is present there.

FIG. 44. Section of one of the extensions attached to the main mass by the isthmus shown.

FIG. 45. Subcutaneous extensions from a carcinoma arising in a papilloma, as seen from the under side: for comparison with fig. 44. The arrow points to one that has rounded up into a cyst.

FIG. 46. Longitudinal section of one of the finger-like extensions shown in fig. 45: for comparison with fig. 44.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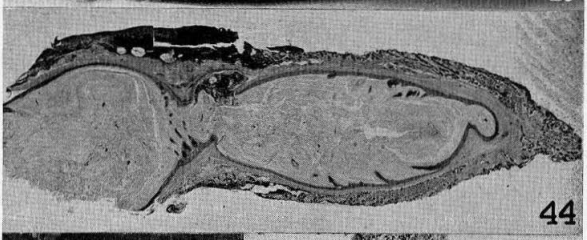
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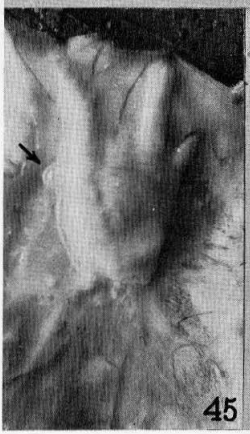
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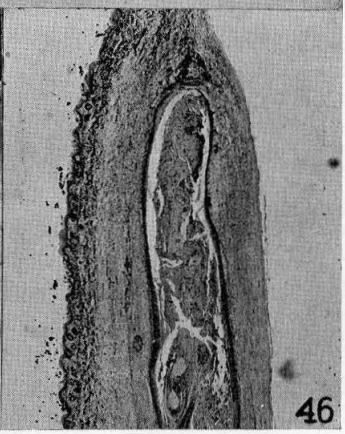
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Under their cumulative influence the papilloma gets more and more out of hand and retrogression becomes infrequent. For weeks before frank malignancy supervenes the growth may appear everywhere to be on tiptoe for cancerous change. It no longer keratinizes into high, vertically striated peaks, but forms low, irregular crusts; and eventually cancer may appear in it at a dozen places at once. There is a period in which many sorts of non-specific interferences, Scharlach R. injection, putting a string through the tissue, local bacterial infection, even simple incision, will precipitate cancer (29). Malignancy can be induced to appear far ahead of the ordinary time by purposeful, local disturbances.

What happens to the virus while all this is going on? It is obviously subjected to extraordinary conditions. Judging from the increased vigor of the growth which is its vehicle of expression, it must undergo some enhancement of activity while the latter is still essentially unchanged. For how else can one explain the fact that the growth, while still only a papilloma, is no longer dependent upon favoring, local conditions for its aggressive activities? Now it will burrow sideways through the normal skin for no apparent reason, forming large, extramural pearls as it never did previously (fig. 36). But virus enhancement will not suffice of itself to explain the cancers. These arise through some further change. And the conditions existing in the papilloma are as if planned to induce variations of the causative virus. A necrotizing virus, vaccinia for example, which kills one cell and then attacks another of the same sort, meets no new conditions save as it encounters defensive measures on the part of the host. The circumstances do not suffice for variation except when the virus is experimentally propagated in an unusual tissue (Ledingham) or enters an animal of a new kind. Then a variant may be formed, smallpox, for example, changing to cowpox in some cases. But a virus which lives with a cell that it does not destroy but urges to proliferation, which has this cell and its successors as a culture medum, so to speak, is subjected to conditions which may conceivably result in variant changes whenever this medium, the cell, is rendered abnormal by external influences. Andrewes

and Shope working with a virus of cottontail rabbits which causes peculiar connective tissue growths of fibromatous appearance have shown that when it has been passed through a series of domestic rabbits it may undergo a variant change which entails an abrupt alteration in the type of disease produced (38).

If the facts could be judged for themselves and the looming shadow of the tumor problem disregarded, one might conclude without more ado that the transformation of the rabbit papillomas to cancers provides an enlightening example of the changes which can take place in a virus on access to a new and more favorable host, in this case the domestic rabbit—changes that find expression in an increasingly active proliferation of the cells upon which the virus acts, followed after a time by the formation of variants of the virus, variants referable to induced alterations in the cells maintaining the virus, and influencing these cells in turn to neoplastic manifestations that in some cases are cancerous. All of the data favor this view. But unfortunately these data cannot be considered for themselves. They open a door to thought and the whole tumor problem crowds in.

Do the facts warrant a discussion of this problem in terms of the virus possibility? It would seem so. For viruses are the nearest causes of tumors now known. Other carcinogenic agents, even the recently purified or synthesized chemical agents, appear to be only preparatory. They bring cells to the brink of neoplastic change, but no evidence exists that they function thereafter, though such evidence has been eagerly sought. They are like the catapult that springs an airplane from the deck of a ship. It provides the plane with the necessary initial velocity and that is all. Viruses actually cause the chicken tumors and determine their character, and the Shope virus causes neoplastic growths which become cancers. Though the part played by the latter is not completely understood, certainly it is responsible for the occurrence of malignancy, continues to exist in the cancers and influences their form.

In the early years of this century the parasitic theory of cancer, so-called, was examined in great detail. Those were the years of belief in cancer houses, cancer regions and cancer epidemics, of

amoebas, yeasts, bacteria, and other living entities that were supposed to cause malignant growths. By an immensity of hard work all these possibilities were ruled out. Viruses had attracted little attention at the time, and their diverse capabilities were unrecognized. It was thought then that the cellular character of tumors, so different from the lesions produced by bacteria and other known infective agents, excluded an extrinsic cause for them. Now we know that some viruses give rise to cell proliferation instead of to necrosis and that certain tumors are actually due to viruses. It used to be urged that such a synchronizing of cell division and parasite division as would assure their continual association could not possibly take place. Now one need only state that it does take place. A study of the books on tumors published during the last 30 years reveals significant changes in points of view. The factual obstacles to a parasitic cause for tumors have been whittled down, but one theoretical difficulty bulks as large as ever. It takes this form: All tumors must have the same cause. Certain benign tumors cannot possibly be due to a parasite, those manifestly referable to developmental anomalies, for example. It is impossible to tell of some tumors whether they are benign or malignant. And so, since some benign tumors cannot be due to a parasite and the benign tumors grade into the malignant, no malignant growth can have a parasitic cause. The argument is not travestied; it is merely stated baldly.

This is a dialectical difficulty, and its initial premise is unsound; for if one fact has become clearer than another it is that all tumors cannot have the same cause. The dermoid cysts, the benign teratomata, the neurofibromas of von Recklinghausen's disease, in short, all of the growths which are obviously the result of embryonic or developmental accidents, carry with them the limitations inherent in their origin. They cannot be placed in the same category with sarcomas and carcinomas, though a sarcoma or carcinoma not infrequently takes origin from the soil they provide.

What real difficulties stand in the way of the supposition, for experimental purposes, that the general run of malignant growths is due to viruses? They can be assembled, some of them from

books, some out of one's own thought, and they are best discussed in one-two-three order so as not to get lost amidst them.

(1) The world-wide occurrence of cancer.

It is plain that the cause of cancer must be present wherever man is. But wherever he goes so do certain of his parasites. He takes with him his colon bacilli and his lice. May he not take viruses as well?

(2) The sporadic occurrence of cancers as attesting to lack of infectiousness.

Tumors are highly conditioned diseases, whatever their nature, dependent upon a concatenation of factors—heredity, age, chronic irritation, and so forth and so forth. The more a disease-producing agent is conditioned in its activity the less will the evidence be, until there is none, that it is infectious in character. The natural incidence of the chicken tumors yields no sign whatever that they are caused by a virus. Their occurrence is highly conditioned and some of them obviously represent a triumph over resistance offered by the host. If all mice were tarred, thus rendering them favorable, mouse cancer would be pandemic.

(3) The failure of the attempts to demonstrate an extrinsic cause for the generality of malignant mammalian tumors.

Frequently virus cannot be obtained from chicken tumors known to be due to it (39), and often the Shope virus cannot be got again from the papillomas of cottontail rabbits, much less from those of domestic animals. In stressing the negative results with mammalian cancers, have technical difficulties been mistaken for a biological principle?

(4) The hereditary determination of tumors.

Tuberculosis was deemed hereditary before the bacillus was recognized. The appearance of malignant tumors of the same sort in identical twins, the cases of hereditary glioma of the retina, and of von Recklinghausen's disease, may mean no more than that when the soil is right, and the contributory circumstances, a carcinogenic agent, perhaps a virus, is effective as it would not otherwise be.

(5) The experimental induction of cancer at sites where it never normally occurs.

The tumors that have given rise to this difficulty, those for example which result from tarring the ears of laboratory animals, are not in the real sense tumors induced at will. Their incidence varies notably from individual to individual; they occur at relatively few places in large areas subjected to carcinogenic stimulation; they are punctate in origin; and though in any one individual their number may increase as tarring or other stimulation is continued, no experimental procedure thus far employed has caused them to appear as diffuse processes or in unexampled multitudes. Some decisive condition or agent is evidently present at the situations where they arise. Andrewes has given reasons for supposing this agent to be a virus entering the organism previously, and ensconced in the epithelium (17) at the time when the carcinogenic substance is applied—an indigenous virus as he terms it.

(6) Cancer does not spring full-blown from normal cells but develops as the result of gradual and often long-continued changes.

The changes, induced by all the various carcinogenic agents, may be of a sort to urge a symbiotic virus or viruses to pathogenic activity. A mere dietary error will bring out a crop of fever blisters on the skin of a man in whom herpes virus has lain latent (40). The virus of lymphocytic choriomeningitis, which exists in the brains of mice that are to all appearances normal, will become active and kill, if a little bouillon is injected intracerebrally (41). By injecting Scharlach R. into virus-induced rabbit papillomas they can be made to keep on growing while untreated growths are retrogressing in the same animal (42).

(7) Metastases of several differing sorts, representative of more than one germ layer, are occasionally encountered in patients dying of a teratoma that becomes malignant.

Many teratomas are supposedly derived from pluripotential sex cells, and if one of these became infected with a tumor-producing virus secondary growths of diverse character would occur as a matter of course.

(8) An enormous variety of malignant tumors exists, deriving as they do from cells of nearly all kinds, and exploiting the wide capabilities of these cells. It is urged that since viruses are highly

specific in their action, one causing osteochondrosarcomas of the fowl for example, another endotheliomas only,[4] an entire microcosm of viruses would be needed to account for all the malignant tumors.

This is an *a priori* objection and the future can be left to take care of it. Medical workers are now beginning to realize through studies of herpes, and submaxillary gland virus, the virus causing lymphocytic choriomeningitis, virus III and others, that the healthy body may have a virus population comparable with that of bacteria but far more considerable and diverse. For whereas bacteria are forced by the body defences to live literally in holes and corners of the organism, upon stretches of mucous membrane or in pockets at situations where antibodies and leukocytes do not get at them, viruses are protected by the very cells that they infect, unless they kill these and thus expose themselves to neutralization by serum and to attack of other sorts. Wherever a cell is, there may a virus live, if symbiosis is enough for its needs or if it merely causes the cell to divide and to go on dividing. The variety of the cells is legion, and life in association with them should infallibly lead to great specialization—just such as exists in the case of the chicken tumor viruses and that causing the rabbit papilloma. Yet the viruses of some chicken tumors have a group relationship, as Andrewes has shown (43), and a single virus of this sort may give rise to tumors that vary not a little within their type (44). Whatever the cause for the rabbit cancers, it acts only upon epidermal cells, and produces changes in these that take a special direction; yet the variety of the resulting tumors—cystic tumors, malignant papillomas, squamous cell carcinomas—is not inconsiderable. The theoretical need for a vast multiplicity of viruses is lessened by such findings.

These are the main factual obstacles to the view that sarcomas and carcinomas can be caused by viruses; and they fade as one looks closely at them.

How far should one be led by the assumption that certain tumors may be due to viruses? Only so far as to make tests with these

[4] A similar specificity obtains in the case of the virus causing the rabbit papilloma.

growths. The tumor problem has withstood the most corrosive reasoning. Yet since what one thinks determines what one does in cancer research, as in all else, it is well to think something. And it may prove worth while to think that one or more tumors of unknown cause are due to viruses.

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