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STUDIES

FROM THE

PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA.

No. X.

THE PATHOGENESIS OF SECONDARY TUMORS

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AND SEPTEMBER 9, 1882.]







THE PATHOGENESIS OF SECONDARY TUMORS.*

IN the present paper I give an account of a series of experiments which bear an important relation to the subject of the "Pathogenesis of Tumors." The work was done in the pathological laboratory of the University of Pennsylvania, and at the suggestion of my teacher in histology, Dr. H. F. Formad.

Some of the results of my work have already been announced by Dr. Formad, in his paper on the "Etiology of Tumors," read before the Pathological Society of Philadelphia, April 28, 1881.†

While engaged in the study of normal and pathological histology, I, like other students in morphology, was impressed by the similarity which the microscope revealed as existing between normal and pathological tissues, namely, the similarity of the cellular constituents of normal tissues and morbid growths. This likeness in constituent elements suggested an analogous mode of development; I therefore assumed that as the normal tissues grow by virtue of the innate cell-activity which characterizes the cell-components of the tissues, pathological tissues develop after a similar process.

When particles of tumors are carried by the lymphatics, they become arrested in the glands, and there usually give rise to sec-

dary growths. This is supposed to be the case with the carcinomata.

The tumors which are supposed to develop secondarily, through metastasis, by means of the blood-vessels are the sarcomata. These, pathologists say, never affect the lymphatic glands secondarily. The blood-vessels in these tumors, having no walls, are mere channels, so that particles are easily carried off, and find their way directly into the circulation, without first going through the lymphatics.

This immediate contact with the circulation also accounts for the fact mentioned by Acker,‡ that secondary sarcoma develops with greater rapidity and energy than secondary carcinoma. Yet the walls of the veins present no obstacle to the destructive encroachment of any truly malignant tumor; they are soon perforated, and the neoplasm creeps along the lumen, and is thus brought into immediate contact with the circulation. Once here, under certain conditions, such as a sudden rise of blood-pressure, a blow, etc., a particle is broken off, and, being swept along by the current of the blood, finally acts as an embolus.

Should the embolus travel in the portal circulation, it generally becomes arrested in the liver; should it be carried by the systemic veins, it usually gets lodged in the lungs.

These principles rest upon experimental and clinical facts.

Cohnheim also claims that secondary tumors are the result of the development of tumor emboli, and he concludes that as the periosteal emboli in his experiments disappeared, there must have existed in the organism of the animal used some power to cause this disappearance. This he calls the power of physiological opposition. According to him, therefore, an individual with metastatic tumors lacks this power, *i.e.*, the tissues surrounding the tumor embolus do not possess a sufficient

* Inaugural thesis to which the alumni prize was awarded at the commencement of the Medical Department of the University of Pennsylvania, 1882.

† In the *Medical Record* for January 14, 1882, will be found an abstract from certain experimental work performed by Dr. M. T. Prudden, of New York. This work, on the subject of "The Origin of the Pus-Cell in Acute Inflammation," was published in full in the *American Journal of the Medical Sciences*, October, 1881.

Dr. Prudden discovered that adult cartilage transplanted may not only not be absorbed, but may continue to grow. In the *Medical Record* this result is given, and an application of it is made to Cohnheim's embryonal theory of tumors; also a comparison is instituted between the experiments of Dr. Prudden and those of Leopold, which latter were published in *Virchow's Archives*, August, 1881. But what the *Record* claims for Dr. Prudden was published as my work, six months prior, in the Proceedings of the Pathological Society of Philadelphia, April 28, 1881, as stated above, and appeared in print in July of the same year, in Dr. Formad's paper.

To the priority of this discovery, therefore, I would lay claim (together with the other results of my work), and I desire to correct the impression which the writer in the *Medical Record* would convey, namely, that Dr. Prudden was the first to make the observations above referred to.

‡ Deutsch. Archiv Klin. Med., xi., 1873, p. 180.

amount of this power to prevent the development of the tumor embolus.

My experiments having shown, *first*, that the periosteal embolus, contrary to the experience of Cohnheim and Maas,* does not disappear in properly-executed experiments, and, *second*, that tumor particles behave in a similar manner, it is evident that the alleged physiological opposition in the tissues of the organs plays no part in the process of metastasis, but everything depends upon the innate vital energy of the embolus.

My experiments further demonstrate that the growth of secondary tumors depends upon the proliferation of the cells of the emboli, and is due exclusively to the emboli themselves, and not to any infection or impression made upon the surrounding tissue.

These thoughts presented themselves in the form of the following questions:

First. Whether tumors can be inoculated by virtue of any specific property, namely, whether they are due to a specific poison residing in juices.

Second. Whether tumors are due to specific cell life, differing in principles of growth and development from that of normal tissues.

Third. Whether tumors are the outgrowth of superfluous or misplaced tissues in the body, and which grow by virtue of ordinary cell life.

For the purpose of acquiring some satisfactory answers to the above questions, I undertook a series of experiments, which gave rather surprising results,—results which, though not in accord with those of distinguished investigators, appear to throw light upon the development of primary and secondary tumors, and, in addition, offer experimental proof of the identity of normal and pathological cell life.

CHAPTER I.

METHODS OF WORK.

The experiments were performed in the pathological laboratory of the University of Pennsylvania, and under the immediate supervision of Dr. H. F. Formad, Demonstrator of Morbid Anatomy in said laboratory.

In order to present clearly the details of experimentation, it will be necessary to describe each class of experiments sep-

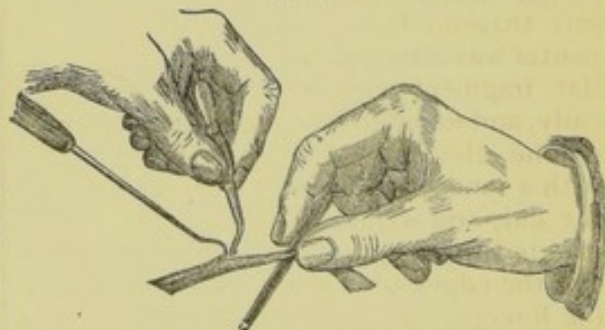
arately, and the first class to which I would direct attention are those performed with *tumor juices*. The animals used were dogs, rabbits, and chickens. Most of the material for experimentation was derived from fragments of tumors removed in the clinic at the University Hospital, and immediately after the removal of the tumor a small piece was taken therefrom and scraped with the back of a scalpel. In this way an average amount of about ten minims was obtained, care always being taken to exclude any particles of the growth. The juice thus obtained was injected by means of a hypodermic syringe into different parts of the animal.

The next class of experiments are those performed with *tumor particles*, which were either transplanted subcutaneously or by means of the jugular vein. As these were made in a manner identical with those in which normal tissues were used, a description of the latter will cover both classes of experiments.

This third class of experiments consisted in the introduction of normal tissues into the circulation.

After thoroughly anæsthetizing the animal, I cut away the hair on the neck in the region of the jugular vein, either right or left, and made a longitudinal cut through the skin and different fasciæ. Coming down upon the external jugular vein, and carefully dissecting it out of its sheath, I passed a grooved director under it, and by pressing the vein between the thumb and the grooved director I was able to control the current of the blood in the vein (see Fig. 1). I then caught up the

FIG. 1.



vein with a pair of forceps, and with a pair of scissors cut obliquely downwards into the vein, below the insertion of the grooved director, thus making a V-shaped incision, with the mouth of the V in the direction of the current. After the cut

* Virchow's Archiv, vol. lxx., 1877.

was made the vein was compressed by an assistant, and the circulation in it temporarily arrested. I next cut down on either the tibia or ulna, where these bones are

the heart if I ligated the vessel in the usual way, by passing a ligature around it above the cut, I tried another mode of ligation which suggested itself, and which proved most successful: while my assistant held the edges of the cut securely with the forceps (see Fig. 2), I passed a ligature directly under the blades of the forceps, taking in only that part of the vessel-wall around the incision (see Figs. 3 and 4). The advantage of such a mode of ligation is that it allows the circulation in the vessel to be continued, so that if the embolus should be caught anywhere it will ultimately be carried onward. After ligation the wound was carefully washed out, cleared of coagula, and then sewed up with silk sutures.

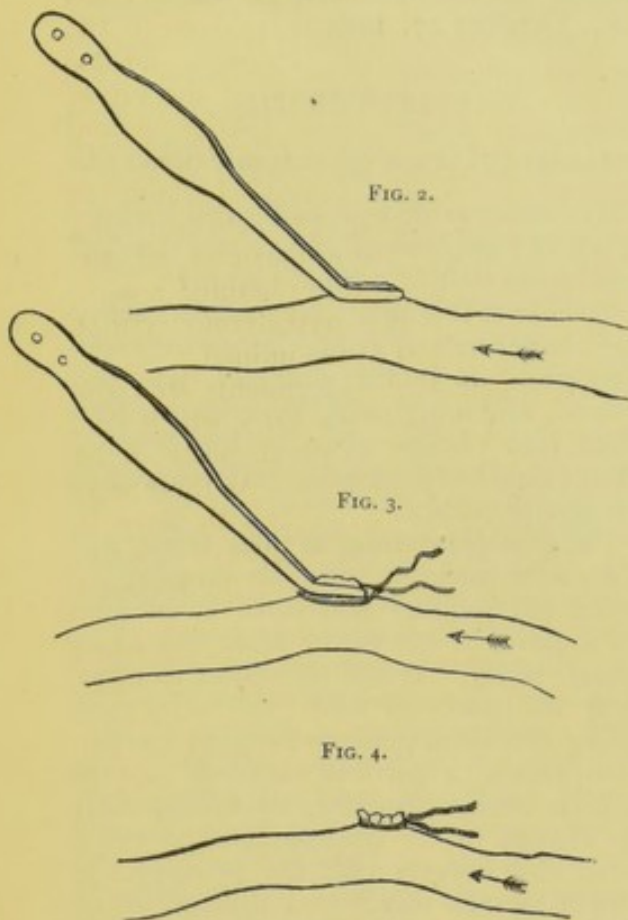
In like manner other normal tissues and tumor particles were introduced. I would also state that the transplantations were made upon the same animals from which the tissues were taken, and not from one animal to another. But in the tumor experiments the particles were transplanted from man to animals. The autopsies in each case were made immediately after the animals were killed, and the specimens were put into preserving fluid, which was either alcohol or chromic acid. Alcohol was to me the most satisfactory, as a too long exposure of specimens to chromic acid renders them brittle.

CHAPTER II.

EXPERIMENTS WITH TUMOR JUICES.

The pathogenesis of tumors in the early history of pathology found expression in views which are far different from those generally held at the present time. One of these views must claim our consideration, as it is still maintained by such high authorities as Paget and Billroth. This view is that there exists in the system a specific virus upon which the formation of malignant tumors depends. It is also maintained by some that this virus resides in the juices of the tumor, and that secondary growths are likewise formed by infection from the blood, contaminated by the juices of the primary tumor.

As far as the medical profession at large is concerned, this idea can be regarded as the one generally prevalent at the present time. (I will refer to this view again in the chapter on Metastasis.)



most superficial, and, pulling aside the tendons, carefully dissected up a small piece of periosteum. The periosteum thus removed was first pressed between the back of my hand and the blade of a scalpel, so as to remove all blood and coagula, and then carefully examined in order to make sure that no bone, tissue, or any foreign matter was attached to it. (An extra similar fragment was examined microscopically, and found to be composed exclusively of the elements of periosteum.) Then with a tenaculum I caught up the edge of the cut, and with a small pair of forceps inserted the fragment of periosteum. After this the edges of the cut were seized with the forceps, and thus the opening in the vein was temporarily closed. Then directing my assistant to remove the pressure from the vein, the blood would rush down its accustomed channel, sweeping before it the periosteum or any other tissue particle that had been introduced. Fearing that the embolus might not be carried down to

Peyrille,* Dupuytren, Valentin, Vogel, and Billroth experimented with tumor juices, and failed to reproduce a tumor by the injection of these juices into the lower animals.

On the contrary, Lebert and Weys,† Langenbeck,‡ Eiselt,§ C. O. Weber,|| Follin and Lebert,¶ claim to have succeeded in producing cancerous nodes in different organs of animals by injecting cancer juice into their circulation.

To ascertain whether there *is* such a specific virus in the juices, I undertook a series of twelve experiments, making injections of tumor juices into different parts of the animals.

The animals were kept under observation for one year, and careful autopsies revealed no trace or effect of the injected juices. The juices were taken from hard and soft cancers, and also from sarcomas. All the experiments were negative, the juices injected proving generally an irritant, which gave rise to an inflammatory process followed by suppuration.

It must be borne in mind that the juices before being injected were all examined, and any particles were carefully excluded.

A microscopical examination of the juices showed the following: numerous compound granule-cells, clusters of fatty degenerated epithelial cells, blood, and a large amount of molecular *débris*, all suspended in a transparent, almost colorless liquid.

These experiments, although by no means conclusive, tend to show that there is no soluble virus, or, in other words, no specific soluble virus, in the juices capable of producing tumors, and that the infectious properties, if any exist, must be sought for in other ingredients of the tumor.

In conclusion, I might add that by inference from the results of my experiments and the numerous experiments of others, I am forced to agree with Formad,** who believes that those experimenters who succeeded in producing tumors by inoculation with tumor juices dealt with juices that contained tumor particles composed of living cells; in which case the tumor was not a result of infection, but of transplantation.

For the literature and a detailed analysis of this interesting question, see the exhaustive monograph, "The Etiology of Tumors," by Dr. H. F. Formad (*loc. cit.*), and the discussion thereon, *Proceed. Path. Soc.*, October 27, 1881.

CHAPTER III.

TRANSPLANTATION OF TUMOR PARTICLES.

Are tumors due to specific cell life, differing in principles of growth and development from that of normal tissues?

To answer this question a series of twenty-eight experiments, consisting of the transplantation of tumor particles, was performed, and only those experiments were taken into consideration in which specimens examined microscopically showed no retrograde change.

The transplantations of these tumor particles were made at intervals ranging between ten minutes and three hours after the removal of the tumor from the living human being. It was my object to transplant the particles while the cells composing them still possessed vital properties. Thus, should a particle continue to exist without being absorbed, notwithstanding the change in its environment, it would prove conclusively that the principles of growth therein manifested differed in no wise from those which govern the growth of the epithelial cells composing a skin-graft, or it would show that the mode of development differed in no respect from that of transplanted normal tissue.

It will be seen that twenty-eight transplantations with tumors were performed: five with scirrhus cancer, seven with encephaloid, four simple epithelioma, four adenoma, one condyloma, seven sarcoma. The transplantations were made in the following positions: sixteen times subcutaneously, three into muscular tissue, one into anterior chamber of eye, two into jugular vein, one into mammary gland. Of all these experiments only two showed positive results; all the rest were negative.†† Of the two positive experiments, I will now give some details (both being lung experiments). In the first of these, the embolus, after fifty-five days, was found in the lung, and measurements showed it to have increased to about three times its original size.

†† The tables of tumor transplantations are here omitted, to save space and large expense.

* Quoted after Zahn, *Congrès International Médical*, 1877, Geneva, 1878.

† Virchow's *Archiv*, xl. pp. 142-532.

‡ Schmidt's *Jahrbücher*, vol. xxv., 1870, p. 99.

§ Prager *Viertelj.*, Bd. 76, 1862, p. 53.

|| *Chirurg. Erfahrungen und Untersuch.*, Berlin, 1859, p. 259.

¶ *Traité Pratique des Maladies Cancéreuses*. Paris, 1851, p. 136.

** *Proceedings of Philadelphia Pathological Society*, Oct. 27, 1881.

Microscopical examination reveals the following: the embolus is seen to be surrounded by a dense fibrous capsule, which includes, besides the cancer embolus, some organized blood-clot. The capsule referred to is in several places in direct union with the intima of the blood-vessels, and in other places it is so thin that the cancer embolus is in immediate contact with the intima. It appears, in fact, that the cancer structure began to proliferate into the structure of the wall of the blood-vessel, although a complete perforation of the wall was not observed.

The embolus, as mentioned before, is partly composed of the original cancer fragment, which is seen in a most active state of proliferation, and partly of the organized blood-clot. This latter shows slight retrograde change in some portions, while the cancer embolus proper does not show the slightest trace of retrograde change. It can also be distinctly seen that the cancer cylinders, which are seen in such perfect and typical condition, penetrate also into the spaces between the connective tissue of the organized blood-clot.

In the second of these positive experiments, of thirty-five days' duration, the transplanted fragment was taken from a mass of cancer of cervix uteri removed by Dr. William Goodell, at the University Hospital clinic. During the transportation of the fragment from the clinic room to the pathological laboratory, the fragment was kept warm, so as to preserve better the conditions of life. A minute fragment of this tumor was introduced into the jugular vein of a dog by the method described. After thirty-five days it was found in the lung, and represented four times the original bulk. Under low magnifying power the embolus is seen lodged in the lumen of one of the ramifications of the pulmonary artery, and in some places appears in close union with the intima of the blood-vessel. In other places the embolus is somewhat retracted from it. The embolus is incompletely surrounded by a fibrous capsule, and is growing independently as a node, not involving or developing from the surrounding lung-structure, being dependent upon the latter only for a supply of nutrition. It does not present any retrograde change, as shown by the good and uniform staining of the cells composing it. In the neighborhood are seen a few beautiful bronchioles, and all around the tissue is perfectly normal, although slightly com-

pressed; examining the specimen with higher power, the details of the foregoing appearances were elucidated. The wall of the artery which contains the embolus was seen intact, and in places where the union between it and the capsule of the embolus was effected, the union was so intimate that it was impossible to see where the capsule ended and where the intima of the blood-vessel wall commenced. This was rendered more difficult by the circumstance that the intima had undergone decided thickening, and showed evidences of inflammatory changes, which had accomplished the union. The capsule of the embolus is composed of a dense, fibrous, vascular connective tissue, apparently intermingled with smooth muscular tissue. As far as the embolus proper is concerned, it represents typically the tumor whence it was taken. It will be remembered that it was a cancer in uterine tissue, and hence the presence of some muscular tissue which forms a part of the bulk of the embolus is easily explained. Between the alveoli of the vascular connective tissue, which are filled with typical cancer cylinders, are seen some fat-vesicles. All the elements mentioned as forming the component parts of the embolus show active growth. This is evident from the cellular proliferation, from the total absence of any retrograde changes, and eminently from the increase in bulk.

Thus, all the transplantations (twenty-six) were failures, except those to the lungs. These failures I attribute to inflammatory processes destructive to the graft, to the setting up of a chronic suppuration, to impaired cell life, due to delay before transplantation, to mechanical disturbance of the graft, due to restlessness of the animal, rubbing against objects, licking the wound, etc.

There can be no doubt that the large size of the graft in many of the experiments had some negative influence upon the result. It is well known that, in skin-grafting, small grafts give better results than large ones. It may be the same in the case of tumor-grafts. Yet any number of negative results does not disprove one positive result.

Nowinsky,* of St. Petersburg, made a series of experiments similar to mine, in which he used fragments of a medullary cancer from nose of dog; twenty-seven

* Med. Centralblatt, 45, 1876.

transplantations on inflamed skin were all negative, and out of fifteen transplantations on normal skin two were positive. In one of these positive experiments Nowinsky introduced subcutaneously on the back of a dog a fragment of cancer. After fourteen days it reached the size of a pea, and in eight months the size of a walnut. At the end of ninth month the dog was killed, and the tumor excised measured three and a half centimetres in diameter.

The second experiment was of the same character. After one and a half months the dog died, and in the cicatrix of the wound a nodule the size of a pea was found. Both these tumors retained the structure of the primary growth.

Nowinsky draws the conclusion that under favorable conditions pieces of cancer introduced under the skin grow. Klenké* and Goujon† also succeeded in inoculating animals with cancer. Thus the possibility of successful transplantation of morbid growths is experimentally established.

Cohnheim‡ properly remarks that it is not remarkable that living epithelial masses from carcinomata continue to grow after transplantation. The question, however, arises whether these transplanted tumor particles grow by virtue of any specific properties residing in the cell or whether the transplanted cell-masses grow on the principle of the grafts. The latter proposition must be the correct one, as the transplanted particles grew centrally in the form of a node, while not a trace of the tumor structure or any tendency towards it was found in the surrounding tissue. In other words, there was no infection of the surrounding tissues. This was also the case with transplanted normal tissue, as will be shown in the succeeding chapter. It developed in its new and foreign position just in the same manner as it does in its native seat. This fact is well demonstrated by my two successful tumor transplantations, and also by the experiments of Nowinsky, in which the transplanted tumor particles grew in the form of nodes.

It is perfectly conclusive to my mind that no specific infection occurs in the so-called secondary malignant growths. They grow, as do normal tissues, from a central point, as in a skin-graft, without transformation or infection of the surround-

ing tissue. Tumors act deleteriously upon the organism by encroaching with their secondary deposit, which are usually of considerable bulk, and tax the nutrition of the economy to the last degree.

Thus I have proved that transplantation with living tumor particles succeeds. That the tumor particle not only retains its vitality, but also its proliferating power. That it grows and decidedly increases in size. Furthermore, I have demonstrated the exact mode of this growth and development, —namely, that the embolus *grows in itself by virtue of ordinary cell vitality, and not through the agency of any specific infectious properties.*

Again, it is evident from my preparations that the cancerous emboli did not make any "specific impression" upon, or implicate the surrounding tissues into, the cancerous growth. Thus the surrounding normal tissue did not furnish any material for the formation of the new growth (except furnishing the blood-supply), but played an entirely passive part, being simply pushed aside and displaced by the cancerous growth.

I will also show farther on that the growth of normal tissue emboli is accomplished in precisely the same manner, and this serves as a confirmatory proof that metastatic malignant tumors develop in exactly the same manner as particles of normal tissue, and consequently develop *by virtue of ordinary cell life, and not by virtue of any specific properties residing in the cells.*

CHAPTER IV.

TRANSPLANTATION OF NORMAL TISSUE.

Simultaneously with the transplantation of tumor particles, a series of thirty-eight transplantations with normal tissue was carried on, in order to discover the fate of such transplanted particles, to see whether they would continue to grow, or whether they would be absorbed after a certain time, as is asserted by some distinguished observers. Thus, should the experiments show that these particles of normal tissue continue to grow and develop in a manner similar to transplanted tumor particles, it would throw light upon the question whether tumors grow by virtue of specific properties residing in the cells, or whether they grow by virtue of ordinary cell life.

From the table given on the following two pages it will be seen that thirty-

* Huser's Archiv, 1843, vol. iv.

† Etude sur quelques points, etc. Thèse de Paris, 1866.

‡ Cohnheim's Allgemeine Pathologie, p. 633.

No. of Experiment.	Date of Experiment.	Kind of Animal used.	Substance introduced.	Where introduced.	Duration of Experiment, in Days.	Result of Experiment.
	1881.					
1	Jan. 10 to Jan. 30.	Large white dog.	Periosteum taken from left radius.	Right external jugular vein.	20	Adhesions were found between the inferior lobe of right lung and the chest-wall, together with marked congestion of the same lobe, which indicated a previous inflammatory process. Nothing could be found of the embolus. Result negative.
2	Jan. 30 to March 4.	Small black dog.	Periosteum taken from left radius.	Right external jugular vein.	33	Found small hard nodule in right inferior lobe, on the surface and near the middle of the lobe. Specimen under the microscope showed bone-tissue. Result positive.
3	Feb. 8 to Feb. 28.	Large white and brown dog.	Periosteum taken from left radius.	Right external jugular vein.	20	There was no trace of the periosteal embolus, and everything about the lung had a normal appearance. Result negative.
4	Feb. 10 to April 1.	Small brown dog.	Periosteum taken from left radius.	Right external jugular vein.	50	Found nodule in right inferior lobe, on posterior surface, about the middle of the lobe. The nodule was cut without maceration, and under the microscope revealed the structure of bone-tissue. Result positive. See Figs. 7 and 8.
5	Feb. 15 to March 19.	Small yellow dog.	Periosteum taken from left radius.	Right external jugular vein.	32	The embolus was nowhere to be found. The lungs were normal. Result negative.
6	Feb. 26 to June 6.	Large brown dog.	Periosteum taken from left radius.	Right external jugular vein.	100	The lobes of the lungs were the seat of many infarctions and scattered centres of ossification. In the left superior lobe was especially one large centre of ossification. Four of the many centres were cut, and, being examined under the microscope, proved to be true bone-tissue. Result positive.
7	March 1 to June 1.	Small bitch.	Periosteum taken from left tibia.	Right external jugular vein.	92	No trace of the embolus could be discovered. Result negative.
8	March 5 to April 11.	Large white poodle dog.	Periosteum taken from right tibia.	Right external jugular vein.	37	Found one small bony nodule situated on the anterior surface of the right middle lobe. Specimen under the microscope proved to be bone-tissue. Result positive.
9	March 24 to June 6.	Large white bitch.	Periosteum taken from right tibia.	Right external jugular vein.	74	Nodule found on surface of right inferior lobe. It was firm and resisting, measuring about 3 mm. ($\frac{1}{8}$ in.) in diameter. On section, proved to be bone. Result positive.
10	April 1 to June 3.	Medium black dog.	Periosteum taken from right tibia.	Right external jugular vein.	63	No trace of the embolus, and everything about the lung seemed normal. Result negative.
11	April 11 to April 30.	White dog (spitz).	Periosteum taken from right tibia.	Right external jugular vein.	19	Found small nodule on the anterior surface of right middle lobe. The specimen, examined microscopically, shows structure of bone. Result positive.
12	April 12 to June 4.	Small brown dog.	Periosteum taken from right tibia.	Right external jugular vein.	53	No trace of the embolus could be found. Result negative.
13	April 13 to May 24.	Black-and-white coach-dog.	Periosteum taken from right tibia.	Right external jugular vein.	41	No trace of the embolus could be found. Result negative.
14	April 19 to June 2.	Medium black dog, shaggy hair.	Periosteum taken from right tibia.	Left external jugular vein.	44	No trace of the embolus could be found. Result negative.
15	April 21 to May 25.	Small black-and-tan dog.	Periosteum taken from left tibia.	Left external jugular vein.	35	Nothing abnormal could be found about the lungs. Result negative.
16	May 4 to May 19.	White spitz dog.	Periosteum taken from left tibia.	Left external jugular vein.	15	Result negative. The embolus could not be found. Probably arrested somewhere in the heart.
17	May 21 to June 8.	Small brown bitch.	Periosteum taken from left tibia.	Left external jugular vein.	18	Result negative.
18	May 19 to June 8.	Large Newfoundland dog.	Periosteum taken from right tibia; also particle of skin.	Right external jugular vein.	20	Result negative.
19	May 20 to June 9.	Small black bitch.	Periosteum taken from right tibia.	Right external jugular vein.	20	Result negative.
20	Sept. 7 to Dec. 6.	Small black-and-tan dog.	Periosteum taken from left tibia.	Left external jugular vein.	70	Found small resisting nodule on surface of right superior lobe of lung. Section revealed true bone-structure. Result positive.
21	Oct. 1 to Nov. 15.	Small black-and-white dog.	Periosteum taken from left tibia.	Left external jugular vein.	45	Found nodule on surface of right inferior lobe of lung. Result positive.
22	Oct. 19 to Dec. 28.	Small black bitch.	Periosteum taken from right tibia.	Right external jugular vein.	70	Result negative.

No. of Experiment.	Date of Experiment.	Kind of Animal used.	Substance introduced.	Where introduced.	Duration of Experiment, in Days.	Result of Experiment.
1881.						
23	Oct. 19 to Dec. 21.	Small yellow bitch.	Periosteum taken from right tibia.	Right external jugular vein.	63	Result negative. No trace of embolus.
24	Oct. 22 to Dec. 11.	Large yellow bitch.	Periosteum taken from right tibia.	Right external jugular vein.	50	" " " " "
25	Oct. 26 to Dec. 21.	Large gray dog.	Periosteum taken from right tibia.	Right external jugular vein.	56	Found resisting hard nodule on surface and edge near apex of right middle lobe of lung. Result positive.
26	Oct. 29 to Dec. 18.	Large black bitch.	Three fragments were introduced.	Right external jugular vein.	50	The animal died of hydrophobia, having been bitten by another dog. It died five days after manifestation of first symptoms. Three nodes were found, besides many scattered centres of ossification. Two of the principal nodes were on surface of right middle lobe, and the other was on the surface of right superior lobe. The two lobes are preserved in alcohol. Result positive.
27	Nov. 1.	Small black-and-tan dog.	Fragments of skin, the dead epithelium having been scraped off.	Right external jugular vein.	...	Result negative.
28	Nov. 4 to Dec. 24.	Small black-and-tan dog.	Skin with horny layer scraped off.	Right external jugular vein.	50	Result negative.
29	Nov. 9 to Dec. 30.	Large black dog.	Skin with horny layer scraped off.	Right external jugular vein.	51	The embolus was found in the right superior lobe of lung near the periphery, encysted in a blood-vessel. It had increased in size, and did not exhibit any retrograde changes. Result positive.
30	Nov. 12 to Dec. 28.	Small black dog.	Periosteum taken from right tibia.	Right external jugular vein.	46	Result negative.
31	Nov. 12, 1881, to Jan. 2, 1882.	Small black-and-tan bitch.	Periosteum taken from right tibia.	Right external jugular vein.	51	Scattered centres of ossification on the surface of all the lobes of the lung. They presented a glistening appearance, and to the touch were firm and resisting. The right middle lobe is preserved in alcohol. Result positive.
32	Nov. 30 to Dec. 24, 1881.	Small black-and-tan dog.	Periosteum taken from right tibia.	Right external jugular vein.	24	Result negative.
33	Dec. 3 to Dec. 17, 1881.	Large black bitch.	Periosteum taken from right tibia.	Right external jugular vein.	14	Found nodule in left inferior lobe of lung. Result positive. See Figs. 5 and 6.
34	Dec. 6 to Dec. 20, 1881.	Small black-and-tan dog.	Periosteum taken from right tibia.	Right external jugular vein.	14	Found nodule in right middle lobe of lung. Result positive.
35	Dec. 10 to Dec. 24, 1881.	Small white bull-dog.	Periosteum taken from left tibia.	Left external jugular vein.	14	Found nodule in right superior lobe of lung. Result positive.
36	Dec. 10, 1881, to Jan. 7, 1882.	Small white-and-yellow dog.	Periosteum taken from left tibia.	Anterior chamber of left eye.	34	After two days the cornea became opaque. A keratitis followed, and the aqueous humor of the anterior chamber became replaced by some new-formed apparently organized material. Result negative.
37	Dec. 21, 1881, to Feb. 2, 1882.	Small black-and-tan dog.	Fragments of unstriped muscular tissue taken from cervix uteri. Removed by Dr. W. Goodell.	Right external jugular vein.	42	Found nodule in right inferior lobe of lung. It had increased in size, and did not show any retrograde change. Result positive.
38	Dec. 23, 1881, to Jan. 28, 1882.	Large black dog.	Fragments of unstriped muscular tissue taken from cervix uteri. Removed by Dr. W. Goodell.	Right external jugular vein.	36	Negative result.

eight experiments were performed with normal tissues, after the manner described in Chapter I., and that out of these thirty-eight sixteen yielded positive and twenty-two negative results.

The emboli put into the jugular vein were found, at the autopsy, in the lungs,—*i.e.*, in positive results. If inserted in the right jugular vein, the emboli, with few exceptions, were found in some one of the

right lobes of the lung; if in the left vein, they were found on the left side. This observation, though not pertinent, is interesting to record, as it would seem to indicate a division in the current of blood. Most of the emboli were found on the surface of the lobes, and seem to have been forced to that position by the pressure of the blood. Some of them found their way to the very edge of the lobes. Macroscopically they were sharply circumscribed, and projected somewhat from the surface of the lobes in the form of nodes. The experiments are of different duration, and the emboli thus present differences in size and outline. Thus, the experiment of nineteen days' duration shows a thin lamella of bone, while the experiment of thirty-three days shows already a distinct small centre of ossification.

The ossification always taking place from the proliferating or internal layer of the periosteum, it naturally followed the line of that layer, which was in many cases tortuous, for, as the periosteum was being swept along through the blood-vessels, it became rolled up and twisted. This accounts for the twisted appearance of some of the nodules. In the next chapter the microscopic details will be considered.

CHAPTER V.

THE FATE AND MICROSCOPIC STRUCTURE OF PERIOSTEUM AND OTHER PARTICLES OF NORMAL TISSUES EXPERIMENTALLY TRANSPLANTED.

The gradual development of the periosteal embolus introduced into the lung of dogs by means of the jugular vein can be perfectly studied, as my preparations represent the different stages. In all the experiments I was careful to take periosteum only, and not to take any bone-structure with it; so that, while removing a fragment of periosteum from the bone, I occasionally examined a similar fragment as to its histological structure, and found it to present appearances which may be thus briefly described. It was composed of two layers,—an outer or fibrous layer, composed of dense fibrous connective tissue, and an inner or so-called osteogenetic layer, made up of areolar connective tissue, rich in cellular elements, also containing some yellow elastic fibres. Both layers were freely supplied with blood-vessels,

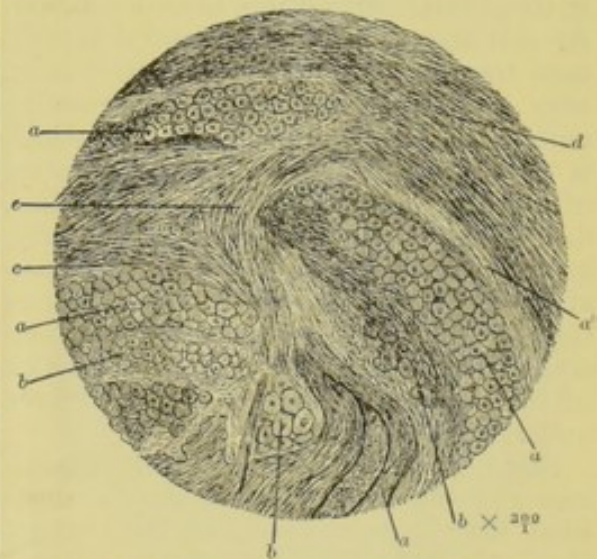
which carried the blood to and from the bone.

Before introducing the periosteum, I took particular pains to squeeze it, so as to free the blood-vessels from clotted blood, in order that, when the embolus finally became lodged in some vessel, the blood might gain access to the interior of the embolus, and in this way give good support and nutrition.

The fate of the embolus was to get lodged in some branch of the pulmonary artery, just as in the case of the tumor emboli. Here, as there, the embolus produced thrombosis; and, if examined a few days after its introduction, it showed itself to be intimately enveloped by a blood-clot, indicating a tendency towards organization. In sections made still later, the organization of this blood-clot demonstrated the higher phases of organization analogous to those seen in ligation of arteries.*

In experiments of fourteen days after preparing the specimens, a section, stained in carmine and mounted in Canada balsam, presented the following appearance.

FIG. 5.



Ossification of periosteal embolus in lung of dog, showing details of the ossifying process. (Experiment No. 34, of 14 days' duration. Drawing reduced to one-fourth of actual size.) *a*. Inner layer of periosteum changed into osteoid tissue. *a'*. Unchanged periosteum. *a''*. Outer layer of periosteum. *b*. Osteoblasts. *c*. Organized thrombus tissue filling interspaces. *d*. Wall of mother vessel in intimate union with embolus. *e*. Band of tissue leading vasa vasorum of mother vessel to the centre of the embolus.

The artery is seen in transverse section, and exhibits slight evidences of inflamma-

* I would even suggest to those who make studies of the healing of arteries to extend their experimentation to similar artificially-produced embolisms of lung.

tory change, the adventitia being thickened and filled with proliferating cells; the media appears normal, while the intima of the vessel shows distinct thickening, also due to proliferation of its cells. In the lumen is seen the periosteum folded up and twisted, and in the interspaces formed by the folds of the periosteum and the walls of the blood-vessels are seen masses of an organizing blood-clot, which in some places are beginning to be absorbed. This organizing blood-clot evidently serves as a matrix for the embolus, the latter being dependent temporarily to a great extent upon the clot for its nourishment. The clot is always in direct communication with the intima, and is in turn nourished by the vasa vasorum of the mother vessel. Only in rare instances is the periosteum seen in contact with, and deriving its nourishment directly from, the vasa vasorum.

At this place the intercommunication of blood-vessels between the embolus and the wall of the blood-vessel is distinctly seen. The outer layer of the lamella of periosteum, as seen in transverse section, is unchanged. The inner layer shows the beginning of ossification analogous to that seen in foetal intermembranous bone-formation. At this stage the inner periosteal layer is seen transformed into hyaline glassy cells, very imperfectly stained, and resembling most perfectly the tissue of callus which is produced during the process of healing of bones. This I will call *osteoid tissue*, designated by authors as the osteogenetic layer. It extends as a uniform belt parallel to and bordering the outer layer of the periosteum. The inmost layer of this osteoid belt is made up of large cells, which in some places are seen distinctly to have undergone calcification.

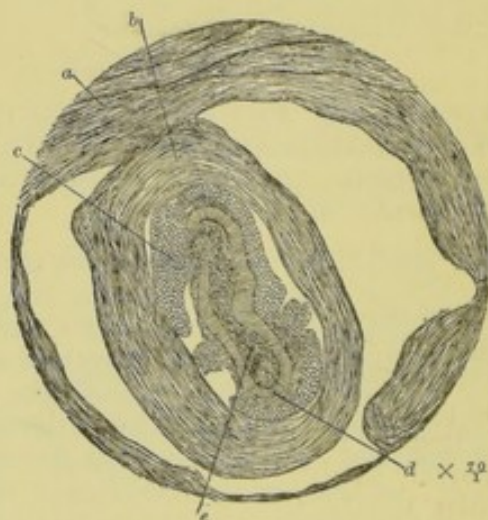
Some preparations made from experiments of the same duration show a somewhat further development of the changes above detailed. Preparations from another of these fourteen days' experiments present the following appearances. The belt of osteoid tissue presents a still more glassy appearance. The outlines of the cells are less distinct, and still did not take carmine staining. The lowest layer of cells has in places unevenly proliferated, forming larger and smaller heaps of cells of osteoid tissue, with distinct calcification; but in the main it continues as a belt, and twists in a curved manner, describing an imperfect ellipse. Next to the osteoid tissue is seen a layer

of cells of embryonic character, many of which are distinctly giant-cells, and this layer also is calcified in some portions. Attached to this layer is a third belt of tissue of very uniform width, and composed of large elongated rod-like cells or plates of uniform size, and arranged nearly parallel with one another, their long axes being perpendicular to the other two layers, so that it presents an appearance similar to that of a lining made up of large columnar cells. This layer and the cells composing it correspond precisely, and have the appearance of what are described as osteoblasts. Within this last belt is a long, narrow space, which is filled with lymphoid cells, osteoclasts, etc., forming the elements of marrow of bone. This collection of cells is freely pierced by blood-vessels.

Outside of this ossifying ellipse is seen the organizing clot upon which the embolus depends for some nourishment. But much of this clot is absorbed, yet enough is left to form a capsular fibrinous mass, being attached on the outside to the intima of the blood-vessel.

It will be noticed that true, fully-developed bone is not seen at this stage.

FIG. 6.



Transverse section of a pulmonary arteriole partly filled with organized blood-clot, enclosing a periosteal embolus, which shows the process of ossification, somewhat diagrammatic. (Drawing reduced to one-third.) *a*. Thickened intima (the other coats of the vessel-wall are not represented). *b*. Clot containing the embolus. *c*. Osteoid tissue. *d*. Layer of columnar osteoblasts. *e*. Marrow-cavity filled with young cells.

In experiments of nineteen days' duration the formation of true adult bone is beginning to become prominent. A lamella of bone substitutes the belt of osteoblasts described above, and the interior of the ossifying embolus is largely composed

of embryonal marrow-cells and calcifying cell-masses.

In preparations from experiments of thirty-three days' duration extensive ossification is seen. The whole periphery of the embolus represents solid, typical bone-tissue with lamellæ, Haversian canals, and bone corpuscles. In the interior of the embolus the development is not completed, and small islands of marrow and calcified masses are yet demonstrable. The outer layer of the original periosteum is seen upon the periphery.

Experiment of forty-five days' duration shows complete ossification of the embolus; only a few angular marrow-spaces are seen in the interior. The growth and further progressive development of the ossifying embolus are evidently accomplished by apposition,—*i.e.*, by superaddition of bone lamellæ. This is seen from the fact that the embolus assumes bulging outlines, and occasionally forms projections of bone-tissue.

In experiment of fifty-six days' duration growth continued. The structure of the embolus answers all the requirements of fully-developed bone. Appositional centres are superadded at the periphery, so that the nodular appearance of the embolus is very conspicuous.

Specimens from experiments of seventy days' duration show beautiful and perfect bone-structure. In the foregoing experiments marrow-cavities were always present, but they became smaller in each successive experiment. Here they are altogether obliterated, leaving only spaces for minute Haversian canals.

Preparations from later experiment continue to present the same general appearances, showing only an increase in bulk. One peculiarity, however, is prominent,—*i.e.*, that the Haversian canals become progressively smaller. Thus the bone is very similar to the so-called *ivory-like* (*eburnated*) bone.

Specimens from experiments of one hundred days' duration show that the embolus has reached at least fifty times its original bulk, and, as in all the later experiments, shows extensive proliferation in all directions.

(I omitted to state the important fact that in most of the later experiments the blood-vessel wall and even the fibrous capsule surrounding the embolus were found to have been completely absorbed, so that

the bony node appeared bare in the midst of the somewhat compressed lung-tissue.)

In experiment of one hundred days' duration, five small independent centres of ossification were found scattered in different parts of the lobe, which contained the main embolus. This latter was found in a branch of the pulmonary artery, which came off near the base of the lobe, so that it is very possible that fragments became detached and gave rise to these secondary nodules.

FIG. 7.

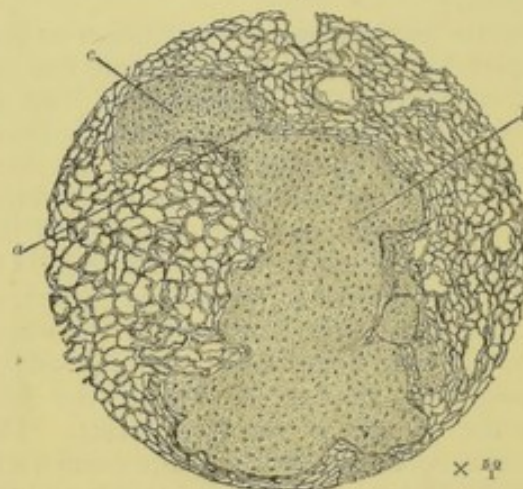
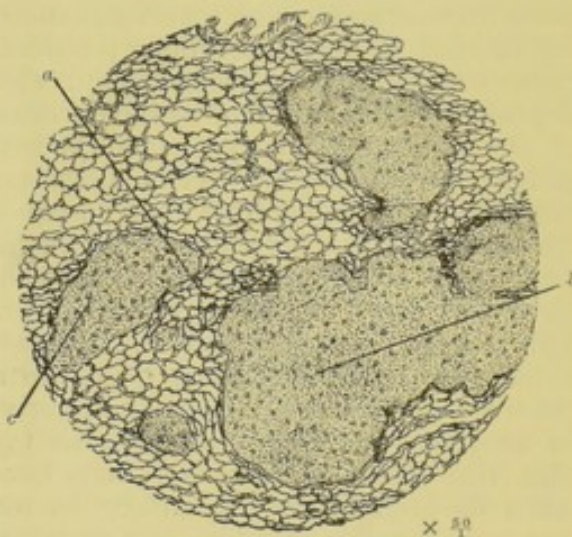


FIG. 8.



Two microscopic sections made from different levels of one of the periosteal emboli developed into bone in lung of dog. (Experiment No. 6, of 100 days' duration. Drawing reduced to one-third of its size.) *a* in Fig. 7 shows connection, *a* in Fig. 8, disconnection, of apparently independent centre of ossification *c*. *b*, Main embolus.

Here I would like to interpret properly the appearance of many apparently independent collateral centres of ossification in the immediate neighborhood of the main embolus. These centres may be noticed in

close proximity with the main centre. By careful study of successive sections of the embolus the reason of this was obtained. It was seen that these centres did have a connection with the main embolus, each being connected by an isthmus. The isthmus is irregular, curving in different directions, so that in a section of the embolus this connection may not be seen, on account of the curve in the isthmus not being reached by the section-knife. The centres thus appear independent. I will refer to this again in a later chapter. (See Figs. 7 and 8.)

Before presenting my conclusion to this chapter I would like to enumerate the details of three other experiments, two of which were performed with adult tissue other than periosteum.

In experiment of thirty-six days' duration, periosteum was introduced into the anterior chamber of the eye of a dog. On making transverse section of the cornea,—*i.e.*, section in the direction of the visual axis,—preparations were obtained which showed the cornea, a part of the iris, and the capsule of the lens intact. The space between the lens and the cornea was seen filled by a new-formed material. In examining this latter there was seen on one side the periosteal fragment surrounded by a dense fibrous capsule, which, although showing increase in bulk and cellular proliferation, exhibited signs of degeneration. This degeneration was indicated by the presence of the products of fatty metamorphosis, such as compound granule-cells, molecular *débris*, etc. Starting from the capsule of the periosteum was seen a new form of inflammatory organized tissue, filling completely the space of the anterior chamber. This tissue was connected by intimate union with the cornea anteriorly, and with the iris and capsule of the lens posteriorly. In fact, this intimate union suggests the idea that the new formation may have taken its origin from the surfaces of the structures mentioned. On close examination it proved to be made up of a vascular areolar connective tissue, infiltrated with pigmented leucocytes.

The outcome of this experiment is that, although the periosteum did not develop itself, it excited enough irritation to set up a slow chronic inflammation, which resulted in the formation of new tissue.

In experiment of fifty-one days' duration, skin was transplanted. In all the

specimens it is clearly seen that the embolus became encysted, and attached itself to the wall of the cyst by means of the subcutaneous connective tissue, while the epithelium of the epidermis remained free in some parts and did not connect itself in any way to the wall of the cyst. The subcutaneous connective tissue shows adipose tissue particularly below the roots of the hairs, looking very much like the so-called "*columnæ adiposæ*." This is the more striking, since before inserting the embolus care was taken to remove most of the subcutaneous connective tissue. The wall of the cyst, which completely encapsules the embolus, is composed of connective tissue, and shows plainly that it has taken its development from the endothelium of the intima. The embolus having been taken from the skin of a black dog, there is to be seen some pigment in the rete mucosum. The hairs are likewise deeply pigmented. Some of the hairs seem to be slightly atrophied and disconnected from their follicles. Pigmented cells are also seen investing the fat-vesicles.

The third experiment to which I have reference is that of transplantation of smooth muscular tissue, taken from a fragment of cervix uteri, removed by Dr. William Goodell, at the University Hospital clinic. (See experiment No. 37 in the table.)

The muscular tissue was examined before introduction, and found to consist of perfectly normal unstriated muscular tissue, and, before introduction, was well squeezed, to rid the blood-vessels of any clots of blood.

As seen from the record in the table, the transplantation was a success. After the lapse of forty-two days the embolus was found of increased bulk, and did not show the slightest retrograde change. As can be distinctly seen in the specimen, the increase in bulk was not in this or any other case due to the presence or superaddition of the organized blood-clot alone, but to an active proliferation of the cells of the transplanted tissue itself. In the embolus under consideration, besides proliferation of the muscular cells, evident from the young cells between the muscular bundles, micrometric measurement reveals increase of the cells.

To the above I may add that the embolus was encapsuled and united with the intima of the blood-vessel in the same

manner as described in other successful experiments.

One point may be mentioned before concluding this chapter; it is this: as already stated, I met with many failures in this work of transplantation, a number of which I did not put on record. Yet, after hitting upon proper methods, as detailed in Chapter I., and becoming accustomed by exercise to carry out properly the details of the procedure, I rarely failed. Thus, in experimenting with muscular tissue, I made but one experiment, and this was positive.

It is a matter of regret to me that I cannot present experiments extending over periods of years rather than months. But, such as they are, they are perfectly satisfactory to me. They have fully established definite laws in the growth and development of transplanted tissues. There is not the slightest reason to suppose that this growth and development should be opposed or hindered. On the contrary, I have full right to conclude that those emboli of normal tissue of periosteum, skin, unstriated muscle-fibres, would, if let alone, have continued to grow, it may be, indefinitely, not having been bound to limits of any physiological purpose as in regeneration. They would have developed into larger tumor-masses. This is the more probable as at no time in the more successful experiments were there any evidences of retrograde changes.

I have also shown that the mode of growth of the emboli of normal tissue was precisely identical with that which I have demonstrated in my experiments with cancer. Conditions, mode of growth, and ultimate results being the same, it naturally follows here, as there, that the development is not due to any specific property of the cells, but is due to the simple vital property of ordinary cell-proliferation.

CHAPTER VI.

REFUTATION OF COHNHEIM'S EMBRYONAL THEORY.

The teachings of Cohnheim on the subject of "Etiology of Tumors" are tersely formulated in the following proposition: "A tumor is the result of a fault or irregularity in the primitive germ."* By this

is meant that in embryonic life, during the period when the tissues are forming out of the cellular material, there is some irregularity in the distribution of this material, by which more cells are set apart for a certain tissue or organ than are needed, and that these cells lie dormant until certain conditions, which are yet problematic, stimulate them to growth.

In support of this theory he brings forward the fact of their hereditary and congenital character, conceding, however, that, according to his theory, it is not necessary that the tumor be always born with the person, but only a predisposition thereto is necessary, which predisposition he regards as a superfluous amount of cells situated in the midst of a tissue, and these cells, by virtue of their embryonic nature, have in them potentially the power of proliferation.

He contends that every child may bring with it into the world the cell-material out of which subsequently a tumor may develop; furthermore, that these superfluous cells may be prevented from proliferating by a *physiological opposition* of the surrounding normal tissues;† but, given a disturbance or destruction of this physiological opposition, a tumor will result. Cohnheim even suggests the probability of many persons dying in whom these superfluous cells existed, but certain unknown conditions, together with a strict physiological opposition, prevented their proliferation.‡

On the other hand, one of the conditions that favor their growth is an increased blood-supply to the part, and this is always met with in the active growth of childhood, the period of puberty, menstruation, or pregnancy. Thus it is easily seen how a relation can exist between the different periods of life and the appearance of new formations,—e.g., tumors of the skin and bones, age of puberty; tumors of the genital organs, time of menstruation and pregnancy.

By means of his theory Cohnheim also explains the peculiarity of tumors as regards their appearance in certain localities. It is a well-known fact that we have new formations at the different orifices where there was a stopping or a union of different blastodermic membranes, as in the rectum, stomach, and uterus.§ Here are favorite

* Cohnheim's Allgemeine Pathologie, Berlin, 1877, p. 635.

† Ibid., p. 661.

‡ Ibid., p. 639.

§ Ibid., p. 641.

seats for new formations, and in these places, according to him, are these superfluous cells especially deposited. Where we have an osteoma in the lung, it is due to a development of cartilage-cells left over from the bronchial plates.*

Thus the germs of every tumor are to be sought for away back in foetal life, and it is therefore to be regarded as a monstrosity; and, as a monstrosity is explained by some disturbance in the primitive germs of the embryo, he maintains that a tumor should also be thus explained.

I have thus far endeavored to present a brief outline of Cohnheim's embryonal theory, together with its application. As is seen, the essence of the theory consists in regarding a tumor as the result of a proliferation of superfluous misplaced (heterotopic) cells, particular stress being laid upon the supposition that these cells are of embryonic character. Impressed with this idea, a number of Cohnheim's followers undertook extensive experiments, and the results of their experimentation seemed to furnish an anatomical basis for Cohnheim's theory. The most successful of these experiments seem to be those of Leopold, whose results I will quote immediately. I would like, however, to state that, several years previous to Leopold, Zahn made experiments and obtained results essentially identical with those of Leopold. It also appears that Zahn was in no way influenced by Cohnheim's ideas. Leopold, who worked under the direct supervision of Cohnheim, experimented with the following tissues. He transplanted both foetal and adult tissues into the anterior chamber of the eye, jugular vein, and abdominal cavity of rabbits. The tissues used were cartilage, bone, skin with hair, intestine, whole extremities with and without hair and nails, whole heart, large pieces of rib, and whole foetal head. From five series of experiments, he draws the following conclusions:

"Transplanted cartilage from adult rabbits is absorbed, or remains in very exceptional cases stationary.

"Transplanted cartilage from foetal living rabbits continues to grow every time, so that it may become two or three hundred times the size of the particles transplanted, thus giving rise to true tumors." These tumors he calls *enchondromata*.

The experimenter describes the mode of development and ultimate fate of each transplanted tissue. In the case of transplanted cartilage, he speaks of the formation of bone with marrow-cavities, etc. A tumor presenting these characteristics he calls an *enchondroma*.

Surely this is not in accordance with standard pathological terminology. A calcified mass of tissue with marrow-cavities would ordinarily pass for bone, and a tumor with such characteristics would properly be called an osteoma. However, his experiments show that embryonic tissues possess eminently the power of proliferation, and that adult tissues only in exceptional cases keep from being absorbed; but my experiments clearly show that adult tissue may also continue to grow,—that periosteum introduced into the jugular vein of a dog will proliferate and form small, bony tumor-masses in the lungs. This is entirely at variance with the results obtained by Cohnheim and Maas,—namely, that adult tissue (periosteum) transplanted became absorbed after twenty days.

Since the publication of the results of my experiments by Dr. H. F. Formad, who read a paper on "The Etiology of Tumors" before the Philadelphia Pathological Society, April 28, 1881, in which he embodied the results of some of my experiments, there have appeared two other papers, which to a great extent confirm my observation.

Prudden experimented with adult hyaline cartilage taken from the head of the femur of a rabbit, transplanting the same into the subcutaneous tissue of other rabbits, and in one case there was an actual new formation of hyaline cartilage. The conclusions which he draws from his experiments are as follows: "That in a rabbit the cells of bits of cartilage transplanted alive may live unchanged for many months, or may lead to the new formation of embryonal cartilage, which may undergo active proliferation."

Ollier, of Lyons, describes a case of successful transplantation of bone, and one of his conclusions is that "transplanted bone is capable of living and growing." What interests me in Ollier's operation is the fact that the transplanted adult tissue was not absorbed, thus confirming my observation that transplanted adult tissues do not disappear. In this respect his experiments have a direct bearing upon this subject:

* Cohnheim's *Allgemeine Pathologie*, p. 644.

still, the ultimate results are not pertinent here, as they refer more to the subject of regeneration.

Thus transplanted adult tissue may continue to grow as well as embryonic tissue, and whatever embryonic cells are potentially able to do lies in the power of any living adult cellular tissue. It is one of the grand principles of modern cellular pathology that all new formations arise from pre-existing cellular elements; and, as the cells of every new formation have their prototype in the living mature organism, it is not unreasonable to suppose that these cells may be the germs of a neoplasm. To say that they arise from embryonal cells alone only removes the problem farther back. The question naturally suggests itself, Where do these embryonal cells come from? Under what conditions are they deposited?—which of course can never be determined. A subject is not explained by putting it beyond our reach: such a treatment merely augments its inexplicableness.

The experiments of Cohnheim and Maas (recorded in *Virchow's Archiv*, vol. lxxix.) are incorrect. They must have been conducted carelessly, as their results could not be confirmed. Cohnheim and Maas failed to transplant periosteum successfully, and they explained their failure upon the ground that the transplanted tissue was not of embryonal character.

I repeated their experiments, and out of a series of thirty-eight found that in sixteen the periosteum continued to develop and did not disappear. I have shown also that adult muscular tissue and skin grew vigorously when transplanted into the lungs. (See Chapter IV.)

And now that it has been proved that adult tissues grow as well as embryonal tissues, the whole theory of the embryonal-tumor development is altogether fallacious, if it must depend for its support upon such results as were derived from the experiments in this direction of Cohnheim and Maas and of Leopold.

CHAPTER VII.

APPLICATION OF RESULTS OBTAINED FROM THE EXPERIMENTS TO METASTASIS AND SECONDARY TUMORS.

The experiments which I have performed and tabulated show that a particle of adult tissue, if dislodged from the

parent mass and carried off by the circulation, may continue to grow and increase in size. The periosteal embolus gets lodged in a vessel too small to admit its passage, and, the circulation in it being maintained, as in a thrombus, by means of the vasa vasorum, it ossifies.

These experiments were repeated after the method of Cohnheim and Maas, but with different results: whereas in my experiments the embolus was found, after the lapse of one hundred days, projecting from the surface of the lung, in the experiments of Cohnheim and Maas, after twenty days, the embolus could no longer be felt externally, but was found, a shrunken mass, without ossification, within the blood-vessel, and after thirty days all trace of it disappeared.

Therefore, having found the embolus after one hundred days increased in size and in a healthy condition,—*i.e.*, without any trace of degeneration,—there can be no doubt that such an embolus may continue to grow indefinitely, and form an abnormal mass of tissue,—a tumor.

The analogy between the process just described and that of metastasis of tumors is very close, and the idea that the embolic process underlies metastasis is by no means new.

By metastasis of tumors we understand the carrying of particles of living tissue through the system by means of the blood-vessels or lymphatics. Pathologists define it as that process by which morbid changes are transferred from one primary diseased part or condition of the body to another.

As to the fact of metastasis there is or can be no doubt or dispute, but as to the explanation of the fact there exists the greatest diversity of opinion.

The humoral pathologic school hold that the cause of secondary tumors is the same as that which produces the primary ones, namely, a dyscrasia, or peculiar unknown diseased condition of the blood or blood-making apparatus. This theory is maintained by Billroth, in his *Surgical Pathology*, where he compares the diathesis of tumor-formation to the scrofulous and tuberculous diathesis. In support of this theory many facts are presented, chief among which is this: that after a tumor has been removed from one part of the body, years later, it may be, a secondary tumor of the same structure as the primary one will develop in some in-

ternal organ. The secondary lesion, according to this theory, is secondary only in point of time, and has no relation with the primary tumor further than that it is the issue of a common cause,—dyscrasia of the blood. Thus the relation is one of time, and in no way anatomical.

This view—once held by the majority of leading pathologists—is now generally discarded, and most conclusive proof against it appears to me in the complete failure to produce tumors when tumor juices free from tumor particles were injected.

The process is now regarded as resting upon an anatomical basis, and the secondary tumors are believed to be the result of the development of tumor emboli. The question of dispute here is whether the emboli infect the surrounding tissue by a species of metabolism, and thus give rise to secondary tumors, or whether they grow centrally and produce tumors by virtue of inherent cell-proliferation. Upon this point I would offer the following: in my experiments with tumor particles the particle transplanted never produced any changes in the surrounding tissue indicating any infection, but, on the contrary, it grew independently if it grew at all. In favor of a central growth of the embolus is also the shape of metastatic deposits. It is generally a known fact, among those who investigate this matter closely, that all secondary tumors grow as nodes, and never at the expense of the surrounding tissue.*

One of the strongest points in favor of an infection or transformation of the surrounding tissue was the observation that, in cancer, around the principal tumor mass in the surrounding connective tissue there existed scattered and isolated cancer-nests. These were composed of epithelial cells, and were observed to have no connection with the main tumor. It was therefore inferred that a peculiar power of transformation emanated from the primary cancer which transformed the surrounding connective tissue into epithelioid elements.

But it has been discovered by Waldeyer and Pagenstecher† that the epithelial cells from a freshly-extirpated cancer possess

the power of amœboid motion. This was supposed to explain fully the appearance of these isolated groups of epithelial cells. Yet these isolated epithelial cancer-nests can be explained in a much more plausible manner, so that the amœboid motion of the cells is not at all necessary.

It is a well-known fact that the proliferation of cancer-growths follows the lymph-channels of the connective tissue. These lymph-channels run by no means in a straight direction, but travel in the most circuitous routes. For instance, a channel may start from a primary focus of cell-proliferation, describe a curve, and again reach the level of the primary focus, at the same time the distal end of the curve being some distance from the starting-point. Under such circumstances, a section made across the growth in a straight direction shows isolated cancer-foci, which are nothing more than the distal ends of the curving lymph-channels filled with cancer-cells. Of this fact I have convinced myself by an investigation of the mode of growth of my periosteal emboli in the lungs, which presented similar appearances in microscopic sections. I frequently saw isolated centres of ossification which I was unable to explain until by careful examination of successive sections I discovered that they were nothing more than transverse sections of extended, curved prolongations from the main or central ossifying embolus. (See Figs. 7 and 8.)

Some of the propositions and views referred to in the different chapters of my paper have been suggested and spoken of properly by various observers, but only on mere hypothetical grounds. I feel happy that I succeeded in my research in furnishing facts and proofs by experiments which appear to give a more firm basis for the explanation of the origin and nature of secondary tumors, and which I trust will help to remove this question from the domain of mere speculation.

In my original manuscript (deposited in the Stillé Library of the University of Pennsylvania) I have embodied twenty-five micro-photographs, taken from my specimens, which prove and demonstrate well all the points brought forward. The high price of printing photographs induced me to limit myself, however, to but a few cuts (accurate copies from the photographs) inserted in this paper.

* In favor of the embolic origin of secondary growths is their nearly exclusive peripheral location in organs, and also the fact that experimentally-produced emboli have a similar location.

† Birch-Hirschfeld, *Patholog. Anatomie*, 1877, p. 118.