

Review Article

Gist of Dr. Katsusaburo Yamagiwa's papers entitled "Experimental study on the pathogenesis of epithelial tumors" (I to VI reports)

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Key words

Carcinomatous medium, folliculoepithelioma papillosum, irritation theory, metastasis, tar painting

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The concept of cancer and inflammation has a long history. Virchow's irritation theory based on human cancer engendered the essential role of inflammation in carcinogenesis. Drs. Yamagiwa and Ichikawa first published a comprehensive paper entitled "Experimental study on the pathogenesis of epithelial tumors" (I report) in 1915 in German, and went on to publish five more reports (1915–1924) under the same title. They succeeded in demonstrating that inflammation is an important carcinogenic factor, and the mechanisms are now being investigated by numerous scientists all over the world. In order to introduce Yamagiwa's work to modern cancer researchers, the essentials of their six reports have been translated into English as a short review. Scientists' comments on Yamagiwa's contribution are attached by way of introduction.

It was a milestone for cancer research when Rudolf Virchow, in Berlin, established "Reiztheorie" (irritation theory) in 1858, based on his numerous histopathological experiments with human cancer tissue.⁽¹⁾ Katsusaburo Yamagiwa, who was originally a pathologist in Japan, studied "Reiztheorie" at the Virchow Institute in Berlin, and after he returned to Japan in 1894 he was appointed full Professor at the Imperial University of Tokyo.⁽²⁾ In 1907 he first established a journal on cancer research, *Gann* (*Cancer Science* at present), in Japan,⁽³⁾ and then conducted experiments based on his idea on chemical carcinogenesis with coal tar on rabbit ears at the Department of Pathology. In 1914 Yamagiwa, with his assistant Koichi Ichikawa, published a preliminary paper "About atypical epithelial growth,"⁽⁴⁾ and then they celebrated great success with a paper entitled "About the artificial production of papilloma," published in the *Proceedings of Japanese Pathological Society*⁽⁵⁾ on 25 September 1915.⁽⁶⁾ Since Yamagiwa loved Japanese *haiku* (a three-lined poem), he expressed his success and satisfaction in 17 Japanese words: "Cancer is identified! Proudly I walk a few steps," which is a well-known statement among cancer researchers.⁽²⁾

In the same year, Yamagiwa and Ichikawa published a comprehensive original report entitled "Experimental study on the pathogenesis of epithelial tumors (the first report)." The paper included protocol, results, transplantation experiments,

concluding consideration and résumé sections, along with his philosophy at the *Mitteilungen* of Medical Faculty, Imperial University of Tokyo.⁽⁷⁾ This first report is an epochal contribution to cancer research. Yamagiwa usually published his reports in German, but also published the text and materials of the first report in Japanese, in 1916.⁽⁸⁾ Remembering Yamagiwa's scientific debut in cancer research society, Folke Henschen from the Karolinska Institute, Sweden, reported in *Gann* in 1968 as follows: Yamagiwa's first communications were published in Japan during the first World War. Therefore, his discovery became known late in Europe. In Germany, he published the main results of his work in Virchow's *Archiv* in 1921 and 1923, but in America his first publication appeared as early as 1918.⁽⁹⁾ This English paper by Yamagiwa and Ichikawa appeared in the *Journal of Cancer Research*, under the title of "Experimental study of the pathogenesis of carcinoma," with 20 figures.⁽¹⁰⁾ The materials in the Japanese paper in 1916 and the English in 1918 vary slightly: The Japanese paper was similar to the first report in 1915, but the English paper in 1918 included results up to 30 June 1916, such as the course and histology of carcinogenesis, and carcinoma cases with metastasis. The German papers from 1915 are not well-known in Japanese cancer society, particularly as the papers were last published in Japanese journals almost 100 years ago. Therefore, in 1965, the Yamagiwa Memorial Foundation

Table III. Carcinoma cases with metastasis

Carcinoma cases	Days of the experiment	Sex	Hair color	Localization of the metastasis	Histological picture of metastasis
IV	366	Male	Black	(a) Lymph node at the root of right ear (b) Submaxillar glands	(a) Cancroid (b) Scirrhus
VI	333	Female	White	Lymph node at the root of right ear	Epithelial layer on the abscess wall
XI/XII	579	Female	Black-white	Lymph node at the root of right ear	Cancroid

published the "Collected Papers on Artificial Production of Cancer," including 13 papers in German, 1 in English and 1 in Japanese, in commemoration of the 50th anniversary of his first paper, published on 25 September 1915.⁽²⁾

Before the success of Yamagiwa, Johannes Fibiger, of Copenhagen University, Denmark, succeeded in producing gastric carcinomas in rats fed on cockroaches, containing *Spiroptera carcinoma* in 1913,⁽¹¹⁾ and the work was easily understood.⁽⁹⁾ I was informed by a journal reviewer that cancers reported by Fibiger were later proved to be granulomas. Henschen reported a story about Yamagiwa's nomination for the Nobel Prize in Medicine as follows: Ludwig Aschoff, from the University of Freiburg, Germany, proposed Yamagiwa for the Nobel Prize in Medicine in 1925, and Henschen commented on the value of Fibiger's and Yamagiwa-Ichikawa's discoveries, but Yamagiwa did not receive the Prize.⁽⁹⁾ However, Fibiger well understood the great contributions of two Japanese scientists – Yamagiwa with coal-tar painting on rabbit ears, and Hidejiro Tsutsui, Chiba University, Japan, with coal-tar painting on mouse skin⁽¹²⁾ – and cited their work in his Nobel lecture, noting that coal-tar cancer develops quite easily among mice, in contrast with *Spiroptera carcinoma*, which develops with great difficulty.⁽¹³⁾ Since then, mouse skin has become a standard tool for experimental carcinogenesis.⁽³⁾ The first report of Yamagiwa and Ichikawa provided a precise histopathological study on the production of folliculoepithelioma papillosum and was the first experimental model of chemical carcinogenesis on rabbit ears based on human pathology: The dried coal-tar crust should be frequently removed by tweezers from the mouse skin, and the newly developed and dilated blood vessels are disrupted. This caused chemical irritation, resulting in the chronic inflammation associated with hyperemia, which was named "carcinomatous medium" by Yamagiwa.⁽⁷⁾ His term suggests that Yamagiwa had already conceived of tumor promotion and progression in studying carcinogenesis on rabbit ears, in light of the Reiztheorie of Virchow.⁽¹⁴⁾

Their first report of 1915 is 50 pages, with 65 references, 41 figures and 6 tables, comprising just one chapter of the book.⁽⁸⁾ Subsequently, Yamagiwa, in collaboration with his colleagues, published five more reports (1915–1924) under the same title, and each report provided advanced original results: They included pronounced carcinoma and cancroid cases, metastasis into vein vessels and lymph nodes, transition stage of cancer, course of cancer stages, and carcinogenesis of mammary gland with injection of lanolin tar. All six reports give more information than the first English paper of the *Journal of Cancer*

Research in 1916. So, I feel, it is now worthwhile introducing the papers in English to Japan and to all of the world: The text has been translated from German to English, referring to the Japanese and English papers in 1916 and 1918. All the significant results are collected in this short review, which emphasizes particularly the main aim of the first report in 1915, along with other significant topics of the other five reports including Tables III and VI with three figures. This review will make it possible to understand the essence of their original reports in English and to enjoy more deeply Yamagiwa's philosophy based on their experiments, which is still vivid in modern cancer research.

Up to the present, numerous scientists have reported on Yamagiwa's significant contributions to cancer research, as well as on his personality, and a brief bibliography has been compiled.^(2,3,6) Notably, Murray J. Shear, of the National Cancer Institute, USA, gave the Yamagiwa Memorial Lecture at the Ninth International Cancer Congress in Tokyo in 1966 and mentioned the three benefits of Yamagiwa's experiment: the right sort of animal (rabbits), the right kind of tar (coal tar) and the fact that the previous researchers had not continued their studies long enough.⁽¹⁵⁾ When the 1st International Awaji Liver Symposium was held in 2005, the Symposium was named the 90-year Anniversary of Katsusaburo Yamagiwa's Innovative Achievement on Carcinogenesis, and a brief page entitled "Revisit: Yamagiwa's carcinogenesis" was presented.⁽¹⁶⁾ The coming year, 2015, will be the centenary of Yamagiwa's epoch-making experiment with coal-tar painting in rabbit ears. When Henschen talked with the distinguished Belgian scientist Dustin, he spoke to him these memorable words: The man who solves the enigma of cancer does not need a Nobel Prize.⁽⁹⁾ This paper will give scientists great encouragement to directly review Yamagiwa's original experiments.

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Experimental study on the pathogenesis of epithelial tumors

(Dedicated to our great, long-venerated Professor Rudolf Virchow)

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Mitteilungen of Medical Faculty of Imperial University of Tokyo 1915; **15** (2): 295–344.

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Introduction

Many decades have elapsed since the Reiztheorie (irritation theory) by Virchow and the theory of stray germs by Cohnheim

were presented. The real cause of epithelial tumors, and, in particular, of carcinoma, was not yet elucidated in the 20th century, although new explanations were continuously proposed. Transplantation experiments with mouse carcinomas were energetically conducted all over the world. Therefore, the pathological anatomical growth of carcinomas was studied using comparative pathology, and biological knowledge was thus further extended. However, these transplantation experiments did not result in further progress with regard to the etiological question: We were not able to artificially induce real malignant epithelial tumors until Fibiger in Copenhagen finally succeeded in the production of papillomas and papilocarcinomas in the stomach of rats at his institute by feeding the rats cockroaches containing larvae (*Periplaneta americana* and *Periplaneta orientalis*); the larvae in the mucous membrane of the stomach in the rats developed first to parents of *Spiroptera*, and then laid eggs. Thus, mother animals and eggs stimulated papillomatous growth in the mucous membrane, and Virchow's Reiztheorie was experimentally proved by Fibiger for the first time; the hypothesis of Borrel was partly proved at the same time. In addition, we already had the interesting examples of rectum adenocarcinoma (Kanamori, Endo) and hepatoma (Kusama), which were caused by chronic irritation of deposited *Schistosoma* eggs. Göbel compiled a comprehensive report on bladder carcinomas, based on *Bilharzia* disease in the urinary bladder. We further began to investigate artificial production of epithelial tumors from last year (1913), and succeeded in finding development of papilocarcinomas on rabbit ears, as we expected. At that time, spontaneous carcinoma was unknown. Although we had not yet come drawn a conclusion from our experiments, we will here briefly summarize the results. We feel it is of primary importance to report the actual answer to the etiological question of carcinoma. Since Yamagiwa published his historical study on the carcinoma-etiology performed for those 10 years in *Nisshin-Igaku* (III, No. 4, December 1913), we will avoid repeating that well-known story.

Real experiments

From April of last year to August of that year (1915).

Because we were informed that the injection of scarlet red oil could not be repeatedly done on the same site, and that the epithelial hyperplasia induced by the injection gradually disappears with time, we continued extensive tar painting. The epithelial growth of the hair follicles was increasingly stimulated with the painting, so we have continued to use the tar painting since April of last year (1914):

The first experimental series (I): A simple tar painting was conducted on the inside surface of 50 rabbit ears every 2 days (in the beginning) or 3 days (later).

The second experimental series (II): A simple tar painting was conducted on the outside surface of 20 rabbit ears, every 2 or 3 days.

The third experimental series (III): A simple tar painting was similarly conducted on the ear edge in cut wounds on 31 ears every 2 or 3 days.

The fourth experimental series (IV): Tar painting was conducted on the outside of 30 rabbit ears, which had been previously injected with scarlet red oil, every 2 or 3 days.

The abovementioned experimental instruction was quite simple. Our experiments demanded only extraordinary patience for a

Table VI. Cases surviving (a) 70 days and (b) 150 days after the beginning of treatment

Experimental series	Number of treated		Number of papilloma bearing ears	% of the number of papilloma bearing ear to that of ear with tar painting
	Animals	Ears		
(a)				
I	15	23	20	87
II	6	6	4	67
III	7	13	7	54
IV	10	10	1	10
(b)				
I	9	13	13	100
II	3	3	3	100
III	4	7	7	100
IV	6	6	1	17



Fig. 6. Multiple folliculoepithelioma papillosum on the inside surface of a rabbit ear, 122 days after tar painting with older animal. (There are a total of 41 figures. Three figures are presented.)

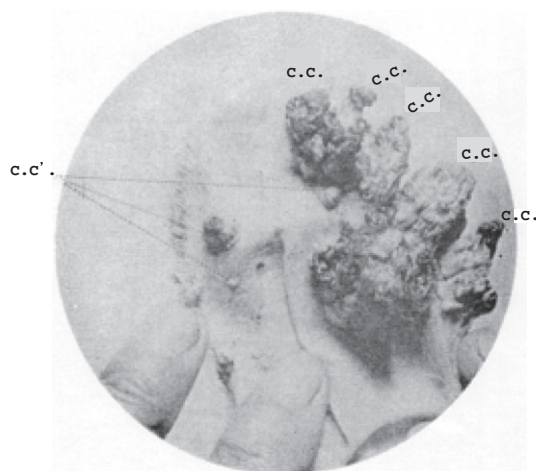


Fig. 9. Skin horns on the inside surface of a rabbit ear, with advanced steep elevated (C.C.) and a few young tumors (C.C').

period of years. The dried tar crust produced by the repeated tar painting was removed with the tweezers every time, so the epithelial plug and newly made or dilated capillaries were often

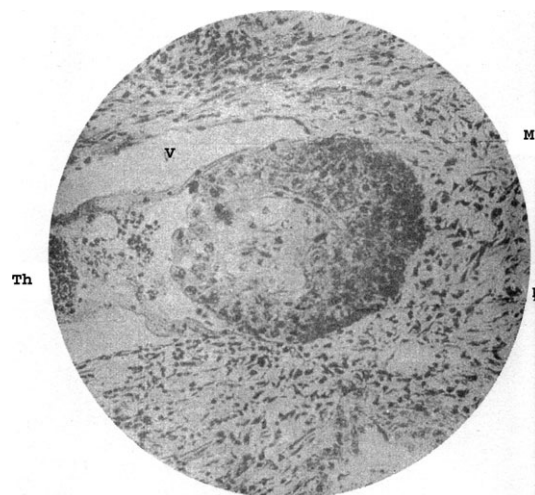


Fig. 31. Tumor thrombosis. Mitosis (M), cluster of carcinoma cells in a vein vessel (V) and thrombus of tumor cells (Th).

disrupted, and small amounts of bleeding and superficial tissue defect occurred. To avoid the boring repetition of the study, the main results will be presented later in the tables. (Note that a summary of the experiment series I–IV is in Table VI, and the representative figures of the experiments are Figs 6, 9, and 31.)

Concluding consideration

I We were delighted to be able to artificially produce both benign folliculoepithelioma, better known as papilloma, and atypical folliculoepithelioma on rabbit ears in our research. They were not produced through some secret procedure, but with simple tar painting, which continued for many months, resulting in chronic chemical-mechanical irritation. The atypical folliculoepithelioma showed infiltrative or heteroplastic deep growth and morphological properties of epithelial cells that were significantly different from that of physiological epidermis.

We were confident of artificially inducing epithelial tumors. Since spontaneous formation of carcinoma and folliculoepithelioma had not previously been found on rabbit ears, we did not need to causal, genetically consider either hereditary disposition or abnormal factors on rabbit ears. There was no difference in gender with regard to the artificial illness of folliculoepithelioma, but we cannot yet decide whether it was a coincidence or whether it was due to sex disposition or something else, but our three cases of carcinoma were all in female rabbits. In addition, the female animal generally lives longer than the male. The hair color seems not to play any significant role, and we can only mention age and individual disposition as inner causes. Young animals do not react to tar painting, but animals over 7–8 months old show similar reactions to “tar scratch.” Hyperemia, presumably a strong itching feeling, epilation and hyperkeratosis appeared. This hyperkeratosis is a physiological symptom of old age in both humans and rabbits. Therefore, we can say that tar painting promotes premature aging of the circumscribed site on the ear; that is, that the tar painting accelerates aging of a distinct part of the skin. Thus, old animals are suitable for the production of folliculoepithelioma, in either benign or malignant nature, as the keratosis of old age appears in combination with tar keratosis. The cutis of old rabbits is inclined to slimy or colloidal

degeneration, judging from human physiology, and certainly supplies a more favorable basis for the deepening growth of atypically growing epithelial cells than the non-degenerative cutis of young animals. Enhancement of keratosis and artificial tar crust causes hyperplasia in epithelial cells of the outside root sheath, especially in the lateral periphery, in the form of sprouts and plugs. This is likely the first cause of papillomatous folliculoepitheliomas. The cartilage layer is directly under the cutis, and this anatomical circumstance is required for the above (and outside) papillomatous growth of our folliculoepithelioma on rabbit ears. When the cutis shows evident slimy metaplasia induced by the action of continuous tar painting, or repeated defect formation with aging or individual disposition of the related animals, the way is paved for the infiltrative deep growth of epithelial cells. In this sense, our histogenetic study on the first production of carcinoma seems to closely approach that of Ribbert. We, along with Ribbert, recognized that epithelial cells gradually acquired a heteroplasieogenic character in the course of heterotopical growth. Slimy degeneration and strong looseness of the cutis induced by injection of scarlet red oil promote the deep atypical growth of hair follicle epithelium, a finding supported by Weigert: We can now explain this as a disturbance of growth balance. Next we will test perforation or extirpation of the cartilage layer with tar painting. However, when the hair follicle epithelia are not provoked to the highest potency of hyperplasia, the deepening growth of the epithelium remains in the slimy, or strongly loosened, cutis, induced by injection of scarlet red oil, resulting in atypical epithelial growth. We do not totally accept the findings of Ribbert, Hauser and von Hanseemann. Specifically, both statements cannot be right: the latter authors believe that epithelial cells become anaplastic on the spot and then easily and deeply grow as carcinoma cells, while the first author states that regenerating epithelial cells acquire carcinomatous characteristic in the course of displacement and heterotopia. The real answer is somewhere in between. Our opinion is as follows: Continuous irritation induces atypical growth of epithelial cells, with the same or similar irritant effects, and the epithelial cells then acquire a heteroplastic character during the heterotopical growth in the loosened neighboring tissue. Yamagiwa named this circumstance "carcinomatous medium," and strongly emphasized this in his study on the production of gastric carcinomas from the simple gastric ulcer or gastric polyps.

We would like to argue that the histological picture of infiltrative growth is not yet conclusive in determining whether or not our folliculoepithelioma is already carcinomatous. In particular, metastasis was absent in our three reported carcinomatous cases, and transplantation experiments in two cases were negative (transplantation in one case was not performed). This argument is probably applicable to the I. Carcinoma-case (No. VI of transplantation) because infiltrative growth is closely connected to simple atypical epithelial growth. However, the displacement of epidermis with the sub-dermal thin layer of cutis through the pressure of epithelial cell nests and clusters in the intra and subcutis, and the invasion of the epithelial cluster into lympho-vessels are unusual for simple atypical epithelial growth. We can only point out that the second case is similar to *ulcus rodens* as an ulcerous cancrioid on a solid base in the beginning, which was proved by Borrmann, who examined the numerous facial carcinomas in the early stages: Metastasis is absent in numerous cases of *ulcus rodens* in humans and burning scar cancrioid. According to the survey of X-ray carcinomas by O. Hesse, metastasis (mainly metastasis of lymph node) was observed in 26% of total carcinomas,

1–4 years after the beginning of carcinoma. Our carcinoma cases on rabbit ears were found just 2–3 months after the first production, too early for metastasis. Therefore, the absence of metastasis does not disturb our diagnosis of *ulcus rodens* on rabbit ears. The third case in No. IV of transplantation was pregnant, so we could easily diagnose cancrioid. Epithelial cell chords and nests consisting of light colored protoplasm with ample mitosis flow everywhere in the sub-dermal depths show numerous typical peals and enter veins (tumor thrombosis), and break through the cartilage layer. In addition, the macroscopically observed type of growth (ulceration, perforation of ear wings) points to a carcinomatous nature. The absence of metastasis and the negative result of transplantation indicate the relatively benign nature of our carcinomas, as the related form cancrioid; especially in tar cancer in humans. Fibiger's papillo-carcinomas in rats are cancers derived from gastric mucous membrane; these are also found in humans, and they are similar to breast carcinomas in mice. They metastasize frequently.

II The inside surface of a rabbit ear does not have papillae, but rather separately standing hairs. The cartilage layer is directly under the cutis. This anatomical-histological circumstance makes the rabbit ear suitable for production of papillomatous folliculoepithelioma through continuous tar painting. Due to the retention of horn substance and continual irritation from the tar, hyperplaseogenic epithelial cells outside the root sheath cause papillomatous multiplication in cutis at the last stage. Epithelial plugs and sprouts do not always grow in the depth (cartilage withstands), but are oblique and lateral. Finally, cornu cutaneum can also occur with folliculoepithelioma, especially with long-survived animals, after the tar painting has been discontinued. Therefore, these skin horns are very interesting, because once the horns are produced after the withdrawal of tar painting, they do not easily diminish, but generally grow more, and new ones will appear beside old ones (compare with protocol: Gr. XI-1, for example).

III We will briefly discuss skin pigment in the production of folliculoepithelioma. When Motegi, on the staff of Yamagiwa, examined penis cancrioids, penis cancrioids were always whitish-grey and pigment free in parenchyma, while the foreskin and penis body were physiologically strongly pigmented. Motegi further reported that the absence of pigment in carcinoma parenchyma is caused by the following: Chromatophores in tumor area of epidermis escape into the cutis, and the carcinoma cells lose the capability to accept supplied pigment. Our experiment with production of folliculoepithelioma on rabbit ears convinced us that Motegi's statement is correct. The mesoblastic chromatophores, which migrate in the epidermis during the early embryonic stage and subsequently share mutual life with epithelial cells, give a certain color to epidermis or the hair. The hyperplastic epithelial plugs and sprouts from the outside root sheath have less pigment, and folliculoepitheliomas are entirely pigment-free. The chromatophores from the area of hyperplasia of hair follicle epithelia migrate in the neighboring cutis, which we directly ascertained under microscope. Consequently, we can speak of the functional derailment of hair follicle epithelia on our folliculoepithelioma, which commonly lose the capability of pigment production. Main pigments will be produced with chromatophores.

Résumé

- 1 Folliculoepithelioma papillosum was artificially produced in 32 of 52 ears of the rabbits (61.5%) over 70 days after continuous tar painting on rabbit ears (Table VI).
- 2 Three cases of folliculoepithelioma papillosum histologically showed typical carcinomatous, infiltrative growth. The infiltration of tumor cells into the veins (tumor thrombosis) and growth through the perforation of cartilage layer were observed in one case. Metastasis was absent in all three cases.
- 3 The real cause of this folliculoepithelioma papillosum and carcinomatosis is tar painting, continued for many months, and is associated with the effective chemical-mechanical irritation. Spontaneous carcinomas and hereditary disposition were absent on rabbit ears. Folliculoepithelioma papillosum and carcinomatosis caused early hyperkeratosis of hair follicles and hyperplasia of hair follicle epithelium.
- 4 The primary hyperplaseogenic epithelial cells of the outside root sheath histogenetically grow into the cutis obliquely and laterally, and produce plugs and sprouts. Cutis connective tissue lying between such epithelial sprouts was raised passively upward with the vessels, in order to deliver stroma and a basis for epithelia.
- 5 The slimy metaplasia of cutis on the folliculoepithelioma carcinomatousum caused by repeated defect formation with tar painting plays an important role in the deep growth of epithelial cells.
- 6 The theory of Yamagiwa was confirmed by our experiment: A newer addition of any specific irritation is not necessary for the production of carcinomas from a precarcinomatous altered basis; only a persistent continuation of the applied irritation is required.
- 7 In our opinion, the strengthening of keratosis, on the one hand, and the looseness of cutis injected with scarlet red oil and the slimy degeneration of cutis observed in a few cases of tar painting on the other, demonstrate that the disturbance of growth balance or a deficiency in growth resistance are more likely the cause of keratosis than the mechanisms of the attraction theory, and the acceptance of soluble lipid substance, the latter of which induces the growth-promoting effect of scarlet red oil.
- 8 Continuously irritated epithelial cells tending to atypical growth will still acquire their heteroplaseogenic characteristic on the way to further growth. Benign folliculoepithelioma usually declines in size, while skin horn made once continues to grow when the tar painting is discontinued.
- 9 Loss and non-formation of pigment in folliculoepithelioma are based on evidence that the chromatophores are ejected from the epidermis and then migrate into the cutis.
- 10 The great significance of age in the production of folliculoepithelioma was confirmed in our experiment. Enhancement of keratosis with tar painting can be understood as an artificial aging of the painted part of the skin.

Experimental study on the pathogenesis of epithelial tumors (II report)

(including 49 pages, 27 figures and 6 tables)
Katsusaburo Yamagiwa and Koichi Ichikawa in 1917.
Mitteilungen of Medical Faculty of Imperial University of Tokyo 1917; **17** (1): 19–67.

Introduction

It is our great pleasure to be able to announce in this second report that we confirmed two metastases into lymph nodes among eight cases of malignant folliculoepitheliomas or carcinomas artificially produced from hair follicle epithelium, using tar painting in our further experiment. We feel the results will certainly satisfy the skeptic. We will discuss the histogenesis of carcinomas in more detail this time, based on our observation of numerous cases of folliculoepithelioma (also known as papilloma): Carcinomas existed in either the first or transition stage of folliculoepithelioma and continued through the histological examination of materials in Experiments I and II.

Synoptic tabular presentation of described cases from Experiments I and II. We artificially produced eight pronounced carcinoma cases among 139 animals (101 of Experiment I and 38 of Experiment II), that is, 5.77%, respectively, 212 ears (137 of Experiment I and 75 of Experiment II), that is, 2.77%.

Formation of metastasis. We noticed the invasion of epithelial cells into lymphatic and blood vessels in many cases of early carcinomas – and in all pronounced carcinomas – but the formation of metastasis and metastasis in the lymph node have been found in only two cases (IV and VI) up to now. Metastasis of lymph nodes in humans was already well-known, but that of our rabbit carcinoma cases was the first found (Table III). Metastasis into the lung and other viscera was not confirmed, while tumor thrombosis in vein vessels was as common as the metastasis in lymphatic vessels. We cannot yet state whether the expected thrombosis of tumor cells disappears through the metabolism. In addition, we do not clearly know the time interval; that is, how many days after the production of carcinomas the metastasis of lymph node will occur. The interval was 66 days in carcinoma case III, about 77 days in case IV, and 72 days in case VI after determining carcinomatous degeneration; that is, the swelling of lymph node at the root of ear.

Experimental study on the pathogenesis of epithelial tumors (III report)

(including 13 pages, 27 figures and 6 tables)
Katsusaburo Yamagiwa and Koichi Ichikawa in 1918.
Mitteilungen of Medical Faculty of Imperial University of Tokyo 1918; **19** (4): 483–495.

This lecture was given at the 7th Conference of Japanese Pathological Society in Tokyo on 5 April 1918.

I. Results

In the firm belief that we can artificially produce carcinomas through continuous tar painting on rabbit ears, we continued our experiment. On 25 November 1915, we reported at the Extraordinary Conference of the Tokyo Medical Society that three cases of carcinoma had been artificially produced. We also reported two new pronounced and numerous beginning cases of carcinoma, along with folliculoepithelioma of the transition stage of carcinoma, at the previous Conference of our Japanese Pathological Society (April 1916). Subsequently, two new carcinoma cases (VI and VII) and the formation of metastasis in the IV (lymph node at the root of ear and submaxillar glands) and VI (lymph node at the root of ear) were reported comprehensively in *Gann* (Vol. 10, No. 4), the *Journal of the Medical Society of Tokyo* (Vol. 30, No. 1, and Vol. 31, No. 6) and the *Mitteilungen of Medical Faculty of Imperial University of Tokyo* (Vol. 15, No. 2, 1915; Vol. 17, No. 1, 1917). Today we will mainly speak about results from April last year to March this year (1917) and demonstrate our preparations.

We experimentally produced numerous pronounced carcinomas, early carcinomas and folliculoepithelioma with the transition stage of carcinoma on rabbit ears until the end of March this year.

IV. Formation of metastasis

At the previous conference (6 April 1916) we were unable to report on the formation of metastasis. After that we observed two cases of metastasis (IV and VI) and reported these to the Tokyo Medical Society in June last year. At the beginning of winter last year, we observed a third case of metastasis (Table III). In carcinoma cases IV and XI/XII, we found the typical picture of canceroid with distinct pearls and the histological picture of the primary lesion.

Concluding sentences

We wanted to determine pronounced, typical carcinomas that can be produced from the physiological epithelial cells through the course of the following stages: atypical epithelial growth, folliculoepithelioma, transition stage to carcinoma and early carcinomas in the beginning. We believe that developed carcinomas can be defeated, like the still benign folliculoepithelioma, by growth competition with connective tissue through the latter, changing into shrinkage or spontaneous healing. According to our results, carcinomas do not develop as carcinomas from the beginning, and do not always continue as carcinomas.

Experimental study on the pathogenesis of epithelial tumors (IV report)

(including 38 pages and 18 figures)

Katsusaburo Yamagiwa and Koichi Ichikawa in 1919. *Mitteilungen of Medical Faculty of Imperial University of Tokyo* 1919; **22** (1): 1–37.

Introduction

We artificially produced canceroid through continuous tar painting on rabbit ears, which became well-known and was later proved with similar results using mouse by H. Tsutsui. Unfortunately, we have not yet heard the opinions of German scientists on our publications up to now, due to the war (1914–1918). F. D. Bullock and G. L. Rhodenburg recently reported in their publication entitled “Experimental carcinomata of animals and their relation to true malignant tumor” that they could not believe our finding of the carcinomatous nature of our experimental canceroids on rabbit ear without actually doing the experiments. We advise them to try tar painting on rabbit ear with great patience. With regard to glandular cancers, Yamagiwa with S. Ohno attempted to produce glandular cancers through the injection of scarlet red oil in the wall of the chicken oviduct. They found three adenocarcinomas among 41 experimental chickens (of tubular gland type after Yamagiwa). Yamagiwa further let M. Takeuchi do an experiment using injection of scarlet red oil in the mammary glands of mice: an adenomatous hyperplasia in male rudimentary mammary glands was observed with many male animals (a periglandular, infiltrative growth in one case). In other results, the canceroid in the artificial cancer of the stomach by Fibiger presents a question, and one case of gall bladder cancer, which was artificially produced by insertion of gall stone containing

radium salt in the gall bladder of experimental animals by Lazarus–Ballow, is not clear-cut. We are firmly convinced that chronic irritation must be considered as one cause of the formation of squamous cell cancers based on multiple studies from the clinical side, and we have worked on experiments with the artificial production of epithelial tumors in mammary glands in order to produce transplantable massive tumors since the summer of last year (1917). Mammary glands located just under the surface of the skin can be easily observed, and are one of the most common sites of carcinoma in humans. Here we will briefly report only the demonstrated results.

Experimental study on the pathogenesis of epithelial tumors (V report)

(including 35 pages and 14 figures)

Katsusaburo Yamagiwa and Koshichiro Maruyama in 1921. *Mitteilungen of Medical Faculty of Imperial University of Tokyo* 1921; **26** (1): 35–69.

Introduction

At the previous *Mitteilung*, Yamagiwa and Ichikawa reported a typical adenocanceroid case and two simple canceroids near the early stage of carcinoma as the result of experiments using injection of lanolin tar, respectively, pure tar, into around the mammary glands of rabbits. In the continuation of the same experiment from April last year (1919) to October 1920, we found a second pronounced case, a third adenocanceroid case in the very early stages, one case of periglandular adenomatous, many cases of adenopapillomatous growth, and five cases of more simple canceroids similar to carcinoma. Although our purpose in producing massive transplantable glandular cancers through the injection of lanolin tar, respectively, pure tar, in the area of the mammary glands or through the nipple directly into the gland was not achieved, we did obtain more simple canceroid cases and a few adenocanceroid cases, as mentioned above, but no real glandular cancer. To summarize the obtained carcinoma cases and precarcinomatous changes: We observed numerous early stage adenocanceroid, and the canceroids from the mammary area appear to show brightening of the cells apart from cornification and excavation of cell cords, respectively, tubes, a pronounced characteristics in adenocanceroid cases.

Experimental study on the pathogenesis of epithelial tumors (VI report)

(including 53 pages and 20 figures)

Katsusaburo Yamagiwa, Koshichiro Maruyama, Kunsei Lee, Tamotsu Fukuda, Riojun Kinoshita, Masatoshi Kashiwagi, and Juntaro Ogawa in 1924.

Mitteilungen of Medical Faculty of Imperial University of Tokyo 1924; **31** (1): 1–52.

Introduction

In this report we will present the results of our experimental study on the pathogenesis of epithelial tumors since the V report: results so far in the experiment with injection of tar, respectively, lanolin tar, into the mamma of rabbit, the relationship between the formation and the growth of artificial tar canceroid on the rabbit ear, and results with painting of coal tar on the back of mouse with or without lanolin feeding.