YAMAGIWA'S TAR CANCER AND ITS HISTORICAL SIGNIFICANCE*1
—From Percival Pott to Katsusaburo Yamagiwa—

Folke HENSCHEN
(Karolinska Institute*2)

It is indeed a great honour for me to read this paper in commemoration of Yamagiwa's discovery of the experimental tar cancer. First of all, I wish to thank Professor Yoshida, my good friend for 30 years, who has offered me the opportunity of giving you a short survey of the attempts to produce experimental cancer, before turning point on this field, from Fibiger's and Yamagiwa's first publications.

I do not think I am wrong if I say that there are two reasons for Professor Yoshida's kind invitation to deliver this lecture. Firstly, I am such an old pathologist — my profession in this speciality began 60 years ago — that I have been deeply involved in the hopelessness and resignation which prevailed among many pathologists after all the innumerable and unsuccessful attempts to produce cancer. Cancer seemed to be something inaccessible, something almost esoteric. On the other hand, I have shared the feelings of new-kindled hope when Fibiger in Denmark and Yamagiwa and Ichikawa in Japan published the first results of their experiments. At that very time, I myself was working in Askanazy's institute in Geneva with unsuccessful experiments to produce cancer by different methods.

Secondly, my connection with the Medical Nobel Committee has given me a fair insight into the first positive advance in experimental cancer.

Almost every great discovery has its precursors. This is also true for Yamagiwa's tar cancer. As Yamagiwa's precursor, one may rightly mention Percival Pott and his publication on chimney'sweep's cancer of the scrotum in 1775. What Pott actually observed was an occupational cancer but, as a matter of fact, it was unintentionally a cancer experiment, carried out during many years. On the other hand, Yamagiwa's cancer was the result of a systematic and purposeful experiment, performed with admirable perseverance. In any case, it seems to me that there exists a direct biological line between Percival Pott's observations in 1775 and Katsusaburo Yamagiwa's experiments in 1915. Within this long space of time, there is another name which should be mentioned; that of the German surgeon Richard von Volkmann who described skin cancer in brown coal tar workers in 1875. Also, Ludwig Rehn deserves to be mentioned in this connection; he was the first to observe cancer in the bladder in aniline workers, in 1885, as a matter of fact, also an unintentional experiment.

*1 A paper read at the Yamagiwa Memorial Lecture, held during the Ninth International Cancer Congress in Tokyo, October 24, 1966.
*2 Karolinska Sjukhuset, Stockholm 60, Sweden.
Today, one is tempted to say, "Isn't it indeed surprising that neither Pott's nor Volkman's observations of authentic and manifest tar cancer of the skin prompted European pathologists in their experiments, and that Japanese pathologists were successful in 1915, 140 years after Pott?"

Yamagiwa was a pupil of Rudolf Virchow. The Japanese Government sent the promising young associate professor to Berlin in 1892, and there he studied pathology in Virchow's institute until 1894. As Professor Ogata pointed out, it can be said that Yamagiwa's contribution to oncology originates largely from his experiences in Berlin and influences of Virchow, dating back to these years. It is of a great psychological interest to follow how Yamagiwa, with an admirable consequence, and in spite of his precocious health, has worked along the line suggested by his teacher, the chronic irritation, and, what Yamagiwa calls his own theory, that there is no need of a new specific factor for the transition of a precancerous state to a real cancer.

Virchow's irritation theory was based on clinical as well as anatomo-pathological experience; at that time, no experiments were carried out. In his classical work, "Die krankhaften Geschwülste" (1863), Virchow points out the necessity to elucidate the various local irritants of different cancers. He looks almost with contempt upon pathologists who trace the cause of cancer back to an unknown and inaccessible X factor, adding that we never will detect this X. The nature of these local irritants must be definitely clarified, Virchow says.

Among these non-specific factors, he devotes several pages in his book to the significance of chronic inflammatory processes as cancer-causing irritants. According to him, Glan had already observed malignant tumors developing from chronic inflammation. At the beginning of the 19th Century, several workers such as John Burns, Broussais, and Carl Wenzel published their work on the same subject.

However, Virchow also emphasized the significance of chemical factors and their capacity to produce cancer after protracted action on epithelial tissue, and he called special attention to the chimneysweeper's cancer and lip cancer.

Experimental attempts to trace the etiology of cancer, to elucidate the pathogenesis of malignancy, gradually started. One could say that they were carried out along three main lines, or have been based on three hypotheses; Virchow's irritation theory, Cohnheim-Ribbert's well-known cellular hypothesis, and the parasite hypothesis. The countless experiments with transplantation of tumors from man to animals and of autochthonous animal tumors are not within the scope of this paper.

Let us begin with the different parasite hypotheses. The great progress in microbiology at the end of the 19th Century led a series of scientists to seek the cause of all types of cancer in infections with bacteria, fungi, algae, and protozoa, or in infestation with animal parasites of different nature. These investigations culminated at the turn of the century. A large number of scientists from France, Germany, Italy, Russia, and Sweden were engaged in such research. I shall only mention a few characteristic work; Nedopil's "Carzinom und Infektion" (1883), Ledoux-Lebard's "Le cancer, maladie infectieuse" (1885), Bra's "Le cancer et son parasite" (1900), Doyen's "Le Micrococcus neoformans et les néoplasies" (1903). I remember clearly when the aged French scientist

448 GANN
Borrel took me aside in Paris, hoping to convince me on the significance of Acarides as carcinogenic factors.

The original parasite hypotheses were soon abandoned but they revived anew, as we know, in the viral hypothesis. As early as in 1908, the Danish scientists Ellermann and Bang demonstrated the cell-free transmission of fowl leukosis, and two years later, Peyton Rous published his well-known experiments, finally rewarded with the Nobel Prize in 1966.

However, the most important and long-standing argument against Virchow's irritation theory came from the numerous supporters of Cohnheim-Ribbert's hypothesis. I heard pathologists speaking a little arrogantly about Virchow's "old" irritation theory as belonging to the past. Cohnheim-Ribbert's doctrine led to numerous experiments, one of the most known is probably Askanazy's experimental teratoids after implantation of embryonal tissue, in which I also was involved. Today Cohnheim-Ribbert's hypothesis must be regarded, more or less, as sheer speculations, in spite of cases of malignant dysontogenetic tumors.

Virchow's irritation theory gave rise to innumerable experimental efforts to produce cancer. I would like to mention some of them. Brosch (1885) injured the skin of his experimental animals, and after some days he treated the wounds with paraffin dissolved in ylene. He repeated the procedure for 2~3 months and produced atypical epithelial proliferations with his method but without any signs of malignancy. Martin's and Albert's experiments with intravenous injections were negative (1885~87). Hanau (1889) tried to reproduce experimentally the skin cancer in paraffin workers. He painted rats during months with raw paraffin but cancer was never produced. Rehn's clinical observations of cancer in the bladder of aniline workers inspired Stoeber to similar experiments. He was able to induce atypical proliferation of the epithelium, but there never arose a cancer. Fischer-Wasels (1905~06) and Jores (1907) treated their animals with scarlet oil and other azo dyestuffs of various composition. Stoeber made use of similar chemical irritants; all these workers succeeded in inducing atypical epithelial proliferation but without any signs of malignant development. All these negative experiments caused an atmosphere of resignation in many quarters. Cancer seemed to remain something inaccessible.

Under such circumstances, the great relief which many pathologists felt when Fibiger published his Spiroptera-induced tumors in rat stomach in 1913 and 1915 is easily understood. Also, here and there existed experiences from non-experimental cancers in connection with infestation by various worms, especially Bilharzia.

It seems not the right place to discuss here the real nature of Fibiger's rat tumors or to try to explain the difficulties to reproduce his experiments. However, it may be said, without reserve, that Fibiger's first publications have had a stimulating influence, also on Yamagiwa and Ichikawa when they carried out their first experiments.

In their first exhaustive paper, published in September 1915, which is dedicated to the memory of Virchow, Yamagiwa and Ichikawa write literary: "Ermuntert durch glorreiche Errungenschaft Fibiger's haben wir auch seit dem Herbst vor—vorigen Jahres (1913) experimentelle Studien über die atypische Epitelwucherung und die künstliche Erzeugung der Epithelgeschwülste angefangen," and now I continue to
F. HENSCHEN

quote them in English, "in order to examine, if Yamagiwa's opinion can be confirmed, that continued irritation can be sufficient for transformation of an atypical epithelial proliferation to carcinoma, without a new secondary factor of specific nature."

All previous experiments with chemical irritation had been successful in as much as they resulted in precancerous states but Yamagiwa's aim was to produce true malignant experimental cancer.

Yamagiwa and Ichikawa were successful. For the first time an indisputable cancer had been produced by a chemical irritant. One easily understands Yamagiwa's feelings when he examined the slides from the ears of his rabbits with papillomas and ulcers, and one reads with emotion in Professor Ogata's Foreword to the Jubilee volume of Yamagiwa's "Collected Papers on Artificial Cancer Production" of 1965, the English translation of a Japanese sonnet (Haiku) that Yamagiwa jotted down on a scrap of paper:

"Cancer was produced!
Proudly I walk a few steps"

Today, there are good reasons to ask "Why was Yamagiwa successful in his experiments whereas so many European scientists had been unsuccessful? Was it the choice of chemical agent, or was it the choice of experimental animals with a special disposition to cancer, or was it mainly Yamagiwa's purposeful perseverance, which gave him his triumph?" Coal tar seems not to have been used in previous experiments, probably the use of this new chemical irritant has been of great importance. Rabbits seem not to be regarded as specially suited for cancer experiments and, as Tsutsui three years after Yamagiwa began painting mice with the same tar, he obtained much more quickly and constantly skin cancer; in some strains of mice he had 100% cancer. In all probability, it was Yamagiwa's patience and tenacity in combination with an adequate chemical agent which helped him to reach his aim.

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 result of his work in Virchow's Archiv as late as 1923, but in America his first publication appeared as early as 1918.

In Europe, his pioneer work attracted enormous attention from all quarters. I could enumerate more than 30 scientists from European countries who hastened to carry out tar painting of various animals by modifications of his and Tsutsui's methods. I only mention Fibiger's and Bang's tar experiments. In a paper written for Freiburg in 1921, Fibiger says, "Needless to discuss the enormous value of these various methods for producing cancer" — he means his own and the Japanese methods — "we have attained a goal, desired long ago, and pursued for a long time which has opened up paths for tumor research and has conclusively proved Virchow's irritation theory."

Aschoff proposed Yamagiwa for the Medical Nobel Prize in 1925, and I was entrusted to express my opinion upon the value of Fibiger's and Yamagiwa-Ichikawa's discoveries. I placed them side by side, emphasizing — I quote myself — "the extremely great value and usefulness of Yamagiwa's method." At that time, I was not a member of the Committee, and the prize was given to Fibiger alone.
YAMAGIWA’S TAR CANCER

Today, 40 years later, I can only express my personal opinion that the Dane and the Japanese should have shared the price. Thirty-five years ago, I discussed with the distinguished Belgian scientist, Dustin, the difficult problems with which the Medical Nobel Committee has to cope, and he said to me these memorable words: “L’homme qui devine l’enigne du cancer n’a pas besoin d’un Prix Nobel” (The man who solves the enigma of cancer does not need a Nobel Prize).

In my opinion, Yamagiwa’s discovery of the tar cancer is of the same importance. Academic prizes cannot increase the scientific value of his discovery. It marks the beginning of a new era in cancer research work.