

## HISTORY OF ONCOLOGY

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# The fascinating germ theories on cancer pathogenesis

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### Summary

For more than 100 years, the germ theory of cancer, proposing that microorganisms were at the origin of the disease, dominated medicine. Several eminent scientists like Etienne Burnet, Mikhail Stepanovich Voronin, Charles-Louis Malassez, and Francis-Peyton Rous argued on the pathogenesis presenting their theories that implicated cocci, fungi and parasites. The impact of these theories was culminated by the No-

bel Prize in 1926 that was attributed to the Danish scientist Johannes Fibiger for his work on the nematode *Spiroptera* as a causative agent in cancer. Even if those theories were the result of fantasy and misinterpretation, they paved the way for the scientific research in oncology.

**Key words:** carcinogenesis, germ theories, Johannes Fibiger, parasitic theory

### Introduction

Apart from the exogenous, strange for today's medical world, misconceptions about cancer (cancer villages, cancer houses, cancer countries, cancer races), the microbial theory of cancer held a significant place in the scientific community during the second half of the 19th century, similarly to tuberculosis during the previous decades. In 1907, Pasteur's follower Etienne Burnet (1873-1960) wrote in his treatise *La Lutte contre les microbes* (The fight against microbes): "Cancer is almost to the point where tuberculosis was, when Villemin demonstrated contagion and inoculability...and now Pasteur gave us a stronger scientific reason; the study of cancer can only be benefited from this. Cancer is inoculated with a fragment of cancer, like tuberculosis is inoculated with a tubercle. Cancer had its Villemin and waits for the discovery of its microbe; it waits for Robert Koch". For cancer villages and cancer houses, Burnet stated: "They point out the contagion; they do not indicate heredity. We had the same illusion on tuberculosis; for a long time a hereditary transmission was believed, without any evidence. After the discovery of bacillus and the ways of contagion, tuberculosis

transmission was explained. It is long discussed for cancer that heredity is a legend that will vanish when contagion will be proved" [1].

### The germs of cancer: coccus and fungi

Several scientists believed that cancerous germ had a preference for wetlands and could be transmitted to humans under favourable conditions, while others supported that the favourite host of cancer could have been the rat, the rabbit or the fish. In many cases, the Pasteur Institute represented by Ilya Ilyich Metchnikoff (1845-1916) and Amédée Borrel (1867-1936), was called to take a position. Bacilli, fungi, sporozoites and viruses were at the core of cancer theory at that time [2].

During 1887 and 1889 Scheuerling and Rappin discovered, independently, intracellular microorganisms (bacilli), which upon culture appeared to contribute to the development of malignant tumours [3]. At approximately the same time, Professor Charles Richet (1850-1935) isolated "micrococcus pyosepticus" [4], and Eugene Doyen (1859-1919) "micrococcus neoformans", which caught the attention of the public, but left the scientific community with mixed opinions [5].

Several scholars investigated the role of certain species of fungi in carcinogenesis. In France, Bra and Charles Mongour (1866-1917) were particularly intrigued by several types of tumours that grow on pears, which could easily be mistaken for malignant tumours. As they explored this concept, they isolated a fungus, "nectria dictissima", from which they prepared an anticancer vaccine. Mikhail Stepanovich Voronin (1838-1903) though, implicated "plasodiophora brassicae" in carcinogenesis, a microorganism that grew on cauliflower roots. His observation caught the attention of Behla who strongly believed that the co-existence of cauliflower and tumours was a mere coincidence. Other researchers were fascinated by certain species of forest mushrooms, to which they attributed the occasional cancer epidemics in woodland areas, a form of cancer that they described as profession-related cancer: the "logger's cancer" [6].

### **Sporozoitic and miasmatic theories of cancer**

At the same time sporozoites were attracting considerable attention, as Charles-Louis Malassez (1842-1909), Joachim Albarran (1860-1912), Jean Darier (1856-1938), Bosc and Mathieu Jaboulay (1861-1913) emphasized their importance in carcinogenesis. In his book *Le Cancer, maladie infectieuse à sporozoaires* (Cancer, infectious disease by sporozoites) [7], Bosc claimed to have dissected several cancerous tumours containing these protozoa. This observation led to the belief that a panspermia could provoke a cancerous growth. Bosc stated that a ubiquitous coccidian, the "coccus oviforme" could have been the pathogen. This could be found in water, ground, most animal species, or even air, but predominantly in rabbit's liver. In the countryside around the farms, the soil was contaminated with spores and cysts rich with carcinogenic coccidia. Contamination of the air and the food chain by this protozoan, could explain the high incidence of cancer in certain rural regions, while the wide use of rabbit liver in several cooking sauces at the time heightened suspicions of its implication in carcinogenesis. Dogs, cats, rats, fowls, amphibians, insects, and fish could have also served as vectors of this "coccus oviforme". Barbel, tench, bassfish, gudgeon and trout were hypothesized on the other hand to be unrelated. The most carcinogenic were thought to be the aquatic animals. Bosc wrote an unusual story: "While a young man was eating a trout felt suddenly a bone penetrating his tongue and immediately he removed a small piece. A few days later, he felt a little discomfort at the point

of penetration, while the fifteenth day he extracted the remaining fragment. From that moment on, the small wound grew and became slightly indurated. Months later, the wound widened, and a carcinoma of the tongue appeared, resulting in the death of the patient ten months after the onset of the disease" [7].

The coccidian theory raised a heated debate. During the 11<sup>th</sup> International Congress of Medical Sciences which was held in 1894 in Rome, Ribbert, André Cornil (1837-1908) and several other scientists strongly opposed against the coccidian theory supporting that the so-called presence of sporozoites in cancerous tumours was simply an optical illusion. Specifically, they thought that the "coccidianists" misinterpreted simple degeneration products for parasites, when looking under the microscope [8]. However, a strange observation directed the research of Pasteur's followers to more original parasite theories. In 1891, a young Parisian scientist, Dr. H. Morau, was working on cancer inoculation studies, while at the same time the experimental study of cancer was developed in London by E. F. Bashford (1873-1923), in Copenhagen by Jensen, in Germany by Paul Ehrlich (1854-1915), and in the Pasteur Institute by Borrel [9]. In all cases, it had appeared that cancer could be transmitted from one subject to another only when the two subjects belonged to the same species, thus suggesting an infectious pattern of transmission. According to Burnet the cell is infected by a "virus" that lives together (symbiosis) with the affected cell and therefore cancer could be a miasmatic disease. This theory was also supported by Amédée Borrel, Pasteur's follower, who became the head director of the Institute of Hygiene of Strasbourg in 1919. Borrel was expert in Parasitology and his research was oriented in tumor's cytology and parasitology. In 1903, he presented his thesis rejecting the various theories on parasite-induced oncogenesis and supported instead the pathogenic role of small nematodes encysted in the tumours [10].

The origins of the virus-related cancer theory could be found in the work of the American scientist Francis-Peyton Rous (1879-1970) (Photo 1), who had studied medicine at Johns Hopkins University and at the University of Michigan. In 1909 he was appointed at the Rockefeller Institute for Medical Research, and one year later, experimentally showed that a virus was responsible for the development of cancer in chicken (Rous sarcoma virus) [11]. While Rous became famous for this discovery, it remained unknown that he was preceded by the French bacteriologist Émile Roux (1853-



**Photo 1.** The distinguished Nobel prizewinning scientist Francis-Peyton Rous.



**Photo 2.** The Danish Nobel laureate scientist Johannes Fibiger.

1933), who, in 1903, in his article published in *Bulletin de l'Institut Pasteur* described a transmissible form of cancer in birds [12].

During 1913, a student of Robert Koch (1843-1910) and Emile Von Behring (1854-1917), the anatomist and physiologist Johannes Fibiger (1867-1928) in Copenhagen, astonished the scientific world by publishing the results of his work on the carcinogenic effect of "spiroptera neoplastica", which was isolated from a captured rat. Specifically, he had demonstrated that there was a parasite, until then unknown, that lives in the muscles of some swarming cockroaches in well-heated buildings, especially in patisseries. Once eaten by rats, the parasite eggs were laid in the rat stomach, and finally excreted in their faeces. Cockroaches, in turn, ate the eggs mixed with faeces. This conclusion was confirmed by dissecting a rat caught in a candy shop in Copenhagen where Fibiger had accidentally discovered the "spiroptera", awarding him the Nobel Prize for Medicine in 1926 [13] (Photo 2).

## Discussion

Many of the theories presented over time on the causation of cancer had both psychosocial basis and implications. For example, the parasitic theory of oncogenesis was likely supported by frightened individuals fearing widespread conta-

gion. In fact, Burnet reported that some children defied their family homes if they had been "hit" by cancer. In 1931, Professor Lumière even spoke of parents avoiding public areas in fear of contacting cancer. Those endorsing the parasite theories argued against the existence of hereditary cancer, since nothing could be done to avoid it, while a series of measures (e.g. improved hygiene and serum therapy) could be taken against a contagious form of cancer. Scientific counter-arguments included the false analogy to tuberculosis, the unorthodox nature of the "cancerous infection" and the almost complete failure of attempts to inoculate cancer.

In the case of tuberculosis, the cause, as well as the mechanisms of pathogenesis and disease progression had been discovered. The pathogen, identified by Robert Koch in 1882, infects the entire body in a perfectly consistent pattern. In absolute contrast, the histopathology of cancer offered a bewildering spectacle anywhere inside the body, as cells suddenly began to proliferate without an apparent reason, and could easily metastasize to other parts of the body. The patient thus, seemed "parasitized by a part of himself". As cancer symptoms may mimic those of any other infectious disease, such as tuberculosis, "pthisic cancer", it follows the course of an infectious disease and ends with cachexia that resembles the cachexia of tuberculosis. But really, what a difference! Tuberculosis

forms many kinds of nodules or tumors schematized by clusters of cells. These cells are mobilized to devour a bacillus that invaded the human body. The cancer cells are moving without an apparent motive, in anarchy, untargeted by immune system cells.

Chance or imagination allows us to speak of “epidemics of cancer” or “cancer houses”. Some pointed out that, if cancer was contagious, the proportion of cancer of the uterus should have been identical to that of penile cancer. However, penile cancer was 20 times less frequent. Others believed they had given rise to malignancies *in vitro*, but it was later shown that they only caused the formation of inflammatory or infectious neoplasias. Certainly Paul Ehrlich in Germany and Bashford, director of the Imperial Cancer Research Fund in London, had proven that, in a few cases, it was possible to transmit cancer from one individual to another. But in these cases the effect was less carcinogenic when the cancer cells were inoculated, than when a cancerous tumour specimen was transplanted or grafted. Cancer could have never been transmitted from one species to another. Within a species, grafting was sometimes successful, but failures far outweighed successes.

Mouse models have been used extensively in these studies. In the beginning of the 20th century, the English oncologist Bashford said that he sacri-

ficed 50,000 mice in order to study cancer. However, different strains of mice presented with different types of response. The gray mouse was, for example, more vulnerable than the white mouse. In addition, when scientists shared their mice for comparative experiments, they found that amazingly, not all had the same tolerance against the transmission of cancer. Thus, while Jensen transmitted cancer in his Danish mice with a success rate of 20-40%, Bashford failed, with only 5 out of 259 London mice developing cancer. Borrel reached a 10% success rate at the Pasteur Institute, but when the French cancer specimens were grafted in English mice, Bashford succeeded in only one experiment out of 78 attempts [14]. These experimental results did not match a pattern of infectious diseases, including tuberculosis, as tuberculosis filtrates give positive results in all cases. Cancer therefore appeared to have distinct pathogenetic mechanisms.

## Conclusion

None of the theories of a microbial and parasitic basis of cancer in the late 19<sup>th</sup> or the early 20<sup>th</sup> century stood the test of time, with the exception of that of Francis-Peyton Rous. Researchers though, had not worked for nothing, as the exploration of wrong pathways, combined with the systematic elimination of the false results, ultimately led along the path of true scientific progress.

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**Correction**

In the article “ Preclinical evidence for the antihyperalgesic activity of CDP-choline in oxaliplatin-induced neuropathic pain “,which appeared in vol.18 (4):1012-1018,2013 issue,the name of the first author posted to Pubmed should be O (Ozkan) Kanat instead of D (Dzkan Kanat).