# Johannes Fibiger and His Nobel Prize for the Hypothesis That a Worm Causes Stomach Cancer

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The 1926 Nobel Prize in Medicine was awarded to Johannes Andreas Grib Fibiger for the subsequently refuted discovery that gastric carcinoma in rats was caused by the nematode *Spiroptera carcinoma*. Fibiger's story is worth recounting not only because it teaches us about pitfalls in scientific research and reasoning, but also because it may provide perverse solace for those of us who will never receive the Nobel Prize (but, of course, deserve it).

## Fibiger's Story

Johannes Fibiger, shown in Figure 1, was born in Silkeborg, Denmark, in 1867 and received his medical degree in 1890 from the medical school of the University of Copenhagen. He went on to earn a doctoral degree in bacteriology from the same university. At 33 years of age, he was named director of the Institute of Pathological Anatomy of the University of Copenhagen, a post he held from 1900 to 1928, the year of his death (1). Fibiger has been described as a meticulous and even obsessive investigator who presented the results of his studies in great detail and with considerable modesty. He was a warm and generous colleague who was widely respected, even by those who disagreed with some of his conclusions (2).

The story of his long fascination with the now forgotten nematode *Spiroptera carcinoma*, mistakenly thought to be a cause of rodent gastric cancer, begins in 1907 with an observation he made while studying stomach papillomas in three wild rats. On sectioning the tumors, Fibiger noted nematodes and concluded that they were the cause of the rodent tumors. While searching the literature on the subject, he discovered an 1878 report in which this same nematode was described as infecting the common cockroach. He then set about trapping other wild rats, examining over 1000 but finding no papillomas. He also trapped 61 rats in an infested sugar refinery located near the institute and found 40 with nematodes in the stomach; 7 of these 40 rats also had growths in the stomach that Fibiger called "cancer." He trapped cockroaches at this same refinery and found that many carried the nematode, but in the larval stage (3).

Fibiger devised an experimental system in which nematode-infected cockroaches were fed to mice and the mice were followed to see if they developed "cancer." In 1919 he reported that he could produce stomach cancer in mice by feeding them cockroaches infected with the nematode in its larval stage (4). He reported a "proportional relationship" between the number of parasites carried by the cockroaches (and then the rodents that ate them) with tumor incidence. He speculated that gastric cancer in humans might be caused by a nematode in the same way that he thought rodents developed this tumor: cockroach + nematode → eaten by rat → rat cancer. The cockroach was considered an "intermediary host" in this schema and necessary for the production of the tumor because feeding mice or rats the *adult* worms did not produce the tumors.

Fibiger named this nematode *Spiroptera carcinoma* and speculated that it was the cause of stomach cancer in both rats and mice. His work was not without contemporary critics. They launched two main arguments against his claims: First, they doubted that he was describing carcinoma in the rat and claimed that he was merely observing hyperplasia. Second, they pointed out that Fibiger had not presented data on the number of rats that became infected by the nematode and never developed cancer and that his "control" group of wild

**Figure 1. Dr. Johannes Andreas Grib Fibiger.**

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rats was not studied concurrently with the experimental group of rats; they complained that he did not report how many rats with stomach cancer failed to demonstrate the presence of *Spiroptera carcinoma* (5). Fibiger's replies to his critics provide an interesting example of evasive argumentation. To the charge that he studied papillomas and not cancer he responded with overwhelming but largely irrelevant detail about the histologic appearance of the tumor; he failed to demonstrate convincingly that it metastasized. Other workers were unable to confirm his findings.

Fibiger never actually declared that he had discovered the cause of human gastric cancer but came perilously close to such an assertion when he wrote: "Helminthes . . . must be assumed to play a greater or lesser role in the development of tumors and cancers in humans." However, in his Nobel Prize lecture he backed off, saying "we are not justified in ascribing to the Helminthes any extensive etiological role in the pathology of cancer in Man" (3).

It took 10 to 26 years for other investigators to conclusively demonstrate the falsity of Fibiger's claim to have discovered a nematode that caused rodent cancer. In 1937, Passey and colleagues (6) reported that Fibiger was probably misinterpreting metaplasia of the lung due to vitamin A deficiency as metastatic cancer from stomach lesions. They postulated that vitamin A deficiency led to metaplasia of the stomach, which was enhanced by the presence of the nematode in the rat stomach; this same vitamin deficiency led to lung metaplasia. Fibiger probably misclassified the stomach hyperplasia as cancer and the lung metaplasia as a metastasis from the stomach lesion, whereas both stomach and lung lesions were probably metaplasia caused by vitamin A deficiency. The photomicrographs they produced were similar to those of Fibiger and they reinterpreted Fibiger's photographs as good examples of metaplasia.

In 1952, Hitchcock and Bell (7) in Minnesota attempted to replicate Fibiger's cockroach-feeding experiments using Sprague-Dawley rats fed diets both adequate in vitamin A and deficient in this vitamin. They concluded that the combination of nematode infestation and vitamin A deficiency led to the development of the large stomach papillomas that had been mistaken for cancers by Fibiger.

A comprehensive and sympathetic review of Fibiger's life and work has been provided by Johannes Clemmesen from Denmark who had the opportunity both to interview persons who knew and worked for Fibiger and to review some of his anatomical slide preparations (8). Clemmesen also believed that Fibiger was mistaking papillomas or hyperplasia, or both, for cancer; Clemmesen himself reviewed slide specimens that Fibiger had classified as cancer and found that they showed hyperplasia.

Clemmesen points out that one of the intellectual foundations of Fibiger's belief that a nematode could cause cancer was based on the 1911 work of Ferguson (9), who described bladder cancer among Egyptians that was associated with schistosomiasis; this was an uncontrolled observation that was uniformly accepted. Thus, the idea that a parasite could initiate or cause cancer had been well delineated before the appearance of Fibiger's 1919 report.

The convention of using concurrent controls postdated Fibiger's work by about 25 years and even now is often overlooked. However, even the use of controls might not have prevented Fibiger from falling into error, because the misclassification of hyperplasia was the real key to his mistaken hypothesis.

Johannes Fibiger was such an admired, thorough, and cautious investigator that his contemporaries seemed reluctant to challenge his assertions. Clemmesen, wondering whether or not Fibiger would have admitted his error and accepted the refutations that followed his death, concludes that Fibiger would have accepted these refutations graciously and in the proper scientific spirit. Perhaps it was fortunate that Fibiger was spared this ordeal.

### Fibiger's Discovery as Seen by His Contemporaries

When attempting to understand how Fibiger was regarded by his contemporaries, it makes sense to start with the speech given by Professor W. Wernstedt, Dean of the Royal Caroline Institute, on presentation of the Nobel Prize to Johannes Fibiger (10). The Staff of Professors of the Caroline Institute express, in eloquent terms, their complete, unrestrained admiration for Fibiger and his work, with such comments as follow:

> Fibiger was the first of these to succeed in lifting with a sure hand a corner of the veil which hid from us the etiology of this disease.
>
> It was therefore possible, for the first time, to change by experiment normal cells into cells having all the terrible properties of cancer. It was thus shown authoritatively not that cancer is always caused by a worm, but that it can be provoked by an external stimulus. For this reason alone, the discovery was of incalculable importance.
>
> But Fibiger's discovery had a still greater significance. The possibility of experimentally producing cancer gave to the particular research into this illness an invaluable and badly needed method, lacking until this time, allowing the elucidation of some of the obscure points in the problem of cancer.
>
> To my mind, Fibiger's work has been the greatest contribution to experimental medicine in our generation. He has built into the growing structure of truth something outstanding, something immortal *quod non imber edax possit diruere*.
>
> You have at the same time given to the study of cancer a method for resolving points which are still obscure. You have stimulated this study as few others have done; you have drawn to its structure new workers who build on your foundations. We may perhaps hope that the day will come when we shall understand the problem of cancer in its entirety. If, on that day, we look back along the hard path we have travelled, your name will shine among the greatest, and you will remain a pioneer and a forerunner.

It is amusing to contrast this outburst of emotion with the perfunctory comments made by the Committee in 1923 on awarding Banting and MacLeod the Nobel Prize for the discovery of insulin: "The Professional Staff of the Caroline Institute has considered the work of Banting and Macleod to be of such importance, theoretically and practically, that it has resolved to award them the great distinction of the Nobel Prize." This very formal statement is preceded by the Institute's qualifications, "We must not imagine that insulin is able to cure diabetes," and "it also has been said that its discoverer was in a preeminent degree favored by lucky circumstances" (11).

Johannes Fibiger was a member of the Swedish Society of Medicine as well as a beloved and respected colleague of the Professors of the Karolinska Institute (some of this faculty influencing the prize award). This explains much of the warmth expressed on the awarding of the Nobel Prize to Fibiger. Affection alone, however, was not the basis for awarding the prize. It appears that the Committee regarded Fibiger's work as a breakthrough on many levels and Fibiger as a pioneer in cancer research. To understand how such an assessment could be made, it is helpful to consider the levels of scientific knowledge and technique in the 1910s and 1920s in the areas of histology, experimental methods, nutrition, and cancer etiology, and to consider how the level of knowledge could introduce errors into Fibiger's conclusions.

## Histology and Pathology in Fibiger's Time

As early as 1918, Bullock and Rohdenburg (5) disputed Fibiger's diagnoses of lesions and asked "whether these might not be interpreted as hyper-regenerative processes rather than as true carcinomata." Fibiger's reputation, methods, and willingness to share slides allowed his diagnoses to stand, and it was not until 1937 and 1952 that Fibiger's diagnoses were finally refuted (6, 7, 12). The Nobel Prize Committee, which was so eager to see the experimental production of cancer, had not been able to verify whether cancer had been produced in Fibiger's laboratory. According to Hitchcock and Bell (7), Fibiger's microscopic diagnoses were repeatedly corroborated by other authoritative contemporary pathologists. Thus, a major error, the misclassification of hyperplasia, was introduced into Fibiger's work, and this can be attributed to the level of technique in histology and pathology in the years 1907 to 1926.

## Experimental Method in Fibiger's Time

Fibiger began his efforts in a scientific world where no success had been achieved in initiating tumor growth in an experimental setting. The ability to produce cancer in a laboratory setting would greatly aid the research into its cure and cause, and thus Fibiger's work was a major effort in experimental cancer research. In the vacuum of previous efforts, any success in "causing" cancer was a breakthrough. Previous researchers had produced very little, which may have been one reason that Fibiger neglected to use controls—animals not exposed to the parasite but fed similar diets. The absence of a control group is a glaring defect to the modern eye, but few of Fibiger's contemporaries criticized him on this ground. Others, doing similar work in the same years, also did not use controls (animals receiving no treatments) in their studies (5). Fibiger's animals were fed a diet of bread and water (assumed by later scientists to be deficient in vitamin A) and exposed to the *Spiroptera* parasite. Had Fibiger studied a control group of animals, he may have found stomach lesions in the absence of exposure to the parasite. Later scientists were able to show that vitamin A deficiencies contributed to the development of stomach lesions in rats (6, 7, 12). The accepted research method of the day, however, did not require Fibiger to study controls, and he was able to conclude that parasites had caused the lesions in the rat stomachs.

A final methodologic limitation of his work was the source of laboratory animals used. He used various strains of wild rats that were not necessarily available to other researchers, which may explain why researchers were unable to reproduce the exact lesions produced by Fibiger. Fibiger acknowledged interspecies variation in susceptibility to lesion induction, but standard strains of laboratory animals were not available at the time (3, 4). The 1937 researchers did not describe their sources for rats (6, 12). In 1952, Hitchcock and Bell used standard strains as well as wild rats caught in Minnesota (7). No researcher has been able to replicate the exact lesions produced by Fibiger, perhaps because of the use of different strains of animals. The variability among experimental animals introduced a lack of precision into the study that was accepted by the scientific community in the early part of this century. It certainly increased the difficulties involved in verifying or refuting results.

## Fibiger's Knowledge of Nutrition

In 1937, Passey and colleagues (6) conducted experiments to show that lesions similar to those produced by Fibiger could be produced by diets deficient in vitamin A. These investigators suggested that the diet of white bread and water, which Fibiger fed to his rats, was deficient in vitamin A. As early as 1924, some researchers speculated that vitamin deficiencies resulted in hyperplasia (13). Fibiger's biographer, Secher, asserted that the bread used in 1907 was made with milk and provided vitamins (2). Such an assertion may have been an attempt to defend Fibiger's work, an attempt that might not have been condoned by Fibiger. In 1952, Hitchcock and Bell (7) corresponded with bakers who believed that white bread made in Denmark in 1907 was probably made without milk or eggs. Thus, the composition of the diet fed to Fibiger's animals is unclear, but the possibility exists that the diets were deficient in certain vitamins and particularly in vitamin A.

Later researchers who produced lesions in response to vitamin A deficiency postulated that vitamin A deficiency explained or contributed to the formation of lesions in Fibiger's rats (6, 7). Although Passey and colleagues (6) attributed the entire effect to vitamin A deficiency, Hitchcock and Bell looked at the interaction

of diet and infection and concluded the following: "Addition of *G[ongylonema] neoplasticum* (*Spiroptera carcinoma*) infection heightens these effects. The corollary fact also was demonstrated, that vitamin A deficiency heightens the effect of the parasites." Thus, the most recent attempt to reproduce Fibiger's work ended with the investigators' acknowledging an effect of the parasite on stomach lesions.

It is not certain that Fibiger's experimental animals were deficient in vitamin A (although it seems likely that some deficiency existed), and the nutritional effect does not necessarily preclude the parasite effect. Although some work on the relation between nutrition and lesions had appeared in the 1920s (13-15), later critics considered it acceptable, given the historical context, that Fibiger's work did not deal with the issue of vitamin A deficiency. Passey and colleagues (6) pointed out that "knowledge of the metaplasia associated with vitamin A deficiency had only been recently recognized," and Cramer (12) similarly wrote "that at that time the significance of the vitamins in nutrition was not as clearly understood as it is now." Fibiger's lack of awareness of nutritional effects may have been typical for the time period and would help explain his research design as well as his conclusions.

## Fibiger's Knowledge of Cancer Etiology

Reading articles published in the 1910s and 1920s, one is struck by two aspects of the scientific community's knowledge of cancer. On the one hand, there was perplexity and mystification, a lack of understanding that did not allow scientists to understand the facts before their eyes. This perplexity was compounded by two factors: the infant state of knowledge of genetics and the desire to apply the infectious model to cancer research. On the other hand, many pertinent facts about cancer etiology had been noted, but scientists were unable to interpret them correctly. With hindsight, one can see how much was already known even before 1920. These two aspects are often revealed in the same paragraph, sentence, or series of logical statements. Professor Wernstedt, in his 1926 speech to Fibiger on the awarding of the Nobel prize, stated the following:

> For example, it had been thought for a long time that a causal connection existed between cancer and a prolonged irritation of some sort, mechanical, thermal, chemical, radiant, etc.; this supposition was supported by the incidence, sometimes verified, of cancer as an occupational disease. Cancer occurring in radiologists, chimney sweepers, workers in the manufacture of chemical products, establish so many examples of cancerous infection that one might believe they were provoked by radioactive or chemical irritations. However, each time experiment was resorted to in an attempt to provoke cancer in animals by irritants of this nature, it failed and the animals refused to contract the disease (10).

In this speech, which reflects prevailing thought, many basic facts were mentioned—for example, that cancer can be an occupational disease and that cancer can be caused by radiation or exposure to chemicals—and then discarded because the theories of the day did not explain the observations, which we now know to be correct.

Fibiger, in his Nobel Prize speech, describes the work of a fellow scientist, Carrel, who succeeded in transplanting tumors by inoculating fowl with cell-free filtrates of tumor tissue (3). Fibiger considered this to be proof that viruses did not play a causative role in cancer. "It is now difficult to uphold the theory that the Rous sarcoma must be attributed to an invisible virus." He then stated, "The carcinogenic properties of the tissue filtrate must therefore be assumed to depend upon the effects of a cellular product, possibly an enzyme" (3). Without knowledge of viruses and their size, Fibiger was perhaps logical in his thinking, but it is another example that the then current level of knowledge prevented scientists from understanding their own observations.

Bullock and Rohdenburg (5) engaged Fibiger (4) in an exchange that further illustrates the confused state of knowledge about cancer. Bullock and Rohdenburg correctly stated that Fibiger had misdiagnosed the lesions and did not produce cancer. They then criticized Fibiger's work on the grounds that his results were contrary to "the recognized laws of malignant tumor growth." They stated that it is generally known that cancer occurs in older people and animals, but that Fibiger ostensibly found cancers in both young and old rats. Bullock and Rohdenburg found that this discrepancy discredited Fibiger's claim of having induced the development of cancer.

Of course, Fibiger had not induced cancer, as Bullock and Rohdenburg stated based on their pathologic analysis, but their further criticisms were based on erroneous assumptions about cancer. Fibiger correctly and effectively refuted their line of reasoning with the following arguments: 1) Observation of tumors in humans does not necessarily correspond with the origin of the tumors; thus, tumors may occur in humans at a younger age than observed. 2) There are well-known exceptions to the rule that tumors occur preeminently in older persons. 3) Some types of cancer ("roentgen ray carcinoma") occur with greater frequency in the young. 4) The existence of a latency period between exposure and cancer may confuse efforts to study the initial effects of an exposure and the relationship of cancer to age (3, 4).

Fibiger was correct in stating that his results were consistent with his observations about cancer, even if they were at odds with generally held assumptions. This ground-breaking attitude was compatible with his role as a leader in the scientific community. The general confusion over cancer etiology, and the lack of supporting data from genetics, virology, and other fields made it easier to overlook truths and to arrive at mistaken conclusions. He was not alone in doing so, and had he lived longer, he might have been one of the first to acknowledge his incorrect conclusions. At the time that he was awarded the Nobel Prize, he had abandoned the parasite method of inducing cancer in favor of the tar-painting method. All the evidence of his life shows that he was dedicated to an understanding of cancer and that he was prepared to move forward with the field.

## Discussion

We now know that gastric cancer is not caused by *Spiroptera carcinoma*, and the purported "discovery" of such a relation hardly seems worth a historical footnote, never mind a Nobel Prize. At the same time, it is quite touching to read the speech given by the Nobel Committee on presenting Fibiger with his award. They considered his work to be a beacon of light in the effort of science to seek the truth. Perhaps his work did serve to inspire other scientists to conduct more research and to persist along the path of human knowledge. Faith in Fibiger's work, belief in Fibiger himself, and the desire for progress appear to have sustained and encouraged cancer research, at least in Scandinavia. Perhaps the Nobel Committee was correct when it stated that "Fibiger has been and will remain a pioneer in this difficult field of cancer research" (10).

Today, his story serves to remind us of the many blind alleys down which science must wander in the search for truth. It also illustrates the ease with which intelligent and educated scientists can mistake illusion for truth. With hindsight, we can spot the blind alleys of yesteryear, but who can say which are the blind alleys of today?

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