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RICHARD EDWIN SHOPE

*1901—1966*

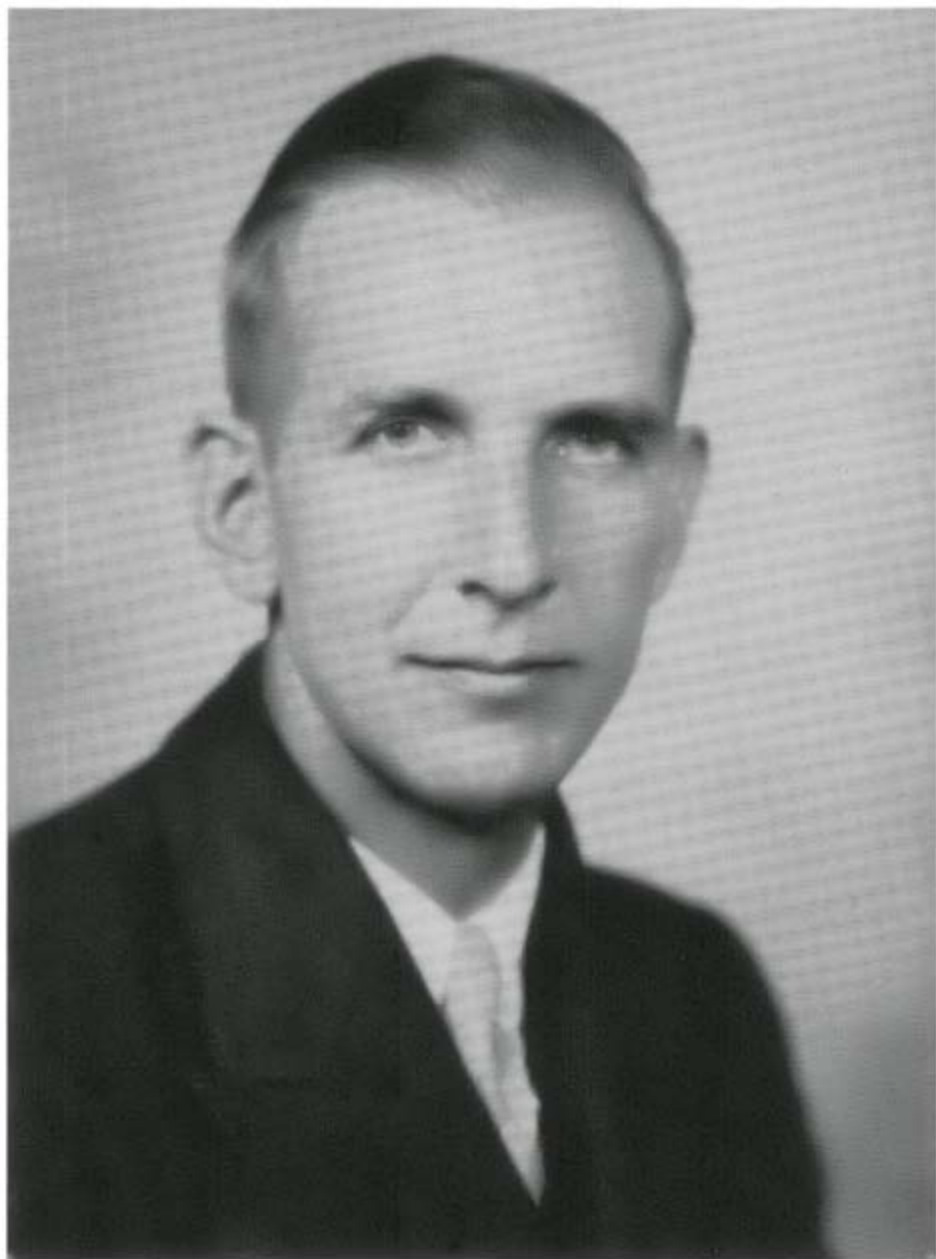
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*A Biographical Memoir by*  
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*Biographical Memoir*

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1941

*Richard E. Shope*

## RICHARD EDWIN SHOPE

*December 25, 1901–October 2, 1966*

BY CHRISTOPHER ANDREWES

**I**N THESE DAYS of fashions in research and dependence upon sophisticated equipment, it is refreshing to know of people like Dick Shope. He was a born naturalist: he found his own problems in the field and sought their solutions there and in the laboratory, using simple techniques. He talked to farmers and veterinarians in his native Iowa and learned from what they had to tell him. In the laboratory he usually worked alone, doing essential things, including post-mortems of pigs, with his own hands.

He was born on Christmas Day 1901 in Des Moines, Iowa. His father was a prominent physician there, and from him and his mother he inherited genes of German, Scottish, English, Pennsylvania Dutch, and Indian origin. He enjoyed an open-air life with hunting and fishing on holidays. From ten onward he earned money by milking cows and looking after farm stock, especially poultry.

At seventeen he went to Ames to register in the School of Forestry, but as the registrar's office was not open, he proceeded to Iowa City and registered as a pre-medical student. At medical school he did well both in his studies and in sports, qualifying in 1924. Thus his college education in medicine and his boyhood experiences on the farm combined to produce a man excellently qualified to contribute to knowledge of animal diseases.

After qualifying, he became an instructor in pharmacology at the University of Iowa and among other activities did work on the chemotherapy of tuberculosis. Because of what he did in that field he was invited to join the laboratories of the Rockefeller Institute at Princeton to work under Dr. Paul Lewis. At this time he married a fellow student, Helen Ellis, and the first few years of their marriage were, financially, difficult ones. Nor was the work on tuberculosis particularly rewarding.

In 1928, however, he left the field of tuberculosis to work on hog cholera and thus began a career in the field of virology that was to continue for thirty-eight years. While investigating hog cholera in the field, Shope saw his first outbreak of swine influenza, and he proceeded to study this, with Paul Lewis, in 1929. They soon isolated a bacterium, *Haemophilus influenzae suis*, similar to Pfeiffer's bacillus, at one time thought to be the cause of influenza in man.

The *Haemophilus* was regularly present in the bronchial secretions of infected pigs, but cultures failed to reproduce the disease. Shope wrote, "We were at this stage of the game, in almost the identical predicament regarding the role of *H. influenzae suis* that investigators of human influenza had been in regarding the Pfeiffer bacillus at the close of the 1918 pandemic."\*

At this time Paul Lewis died of a yellow fever infection contracted in the laboratory, and Shope carried on by himself. He now made sterile filtrates of infectious material and administered them to swine intranasally. The filtrates did indeed produce symptoms but nothing as severe as real swine flu. A few had fever, some coughed, and most had apathy and loss of appetite. Leukopenia was regularly present. Sacrificed animals had changes in the lungs, but whereas swine flu victims showed extensive collapse, bronchitis, and bronchiectasis, those suffering

\* Ricketts Lecture, 1964. See Bibliography.

from what Shope now called "filtrate disease" had minimal changes. It seemed likely, however, that a virus was concerned. Shope later wrote, "Instead of one agent . . . of possible etiological importance, here were two such agents."\* Now, to quote G. W. Corner, "Acting upon an improbable conjecture, Shope administered the bacillus and the virus at the same time, whereupon the animals amazingly came down with typical influenza characterised by severe pneumonia."†

Shope naturally wondered whether his findings had any bearing on the causation of influenza in man. He had not long to wait; in 1933, two years after he had described his findings, Wilson Smith, Patrick P. Laidlaw and I reported that a virus from human influenza would infect ferrets. I then visited Princeton and compared notes with Shope, thus beginning a very close friendship that endured until his death. Over the years we exchanged many long, highly controversial, and often hilarious letters about all aspects of influenza and many other subjects.

After 1934 there followed a period of consolidation in the swine flu work. Recovered pigs were found to develop neutralizing antibodies and to be immune to reinfection. The disease was found to pass readily from pig to pig by contact, but curiously enough, though the virus and *Haemophilus* would pass together from a swine flu-infected pig, only the virus was transmitted in subsequent serial contacts. Then, only the filtrate disease appeared unless the contact pig happened to be carrying the *Haemophilus*.

It was soon shown that swine flu virus, like the human one, would infect ferrets, and the further, important fact emerged that when it was given intranasally to anesthetized ferrets, they developed pneumonia instead of only nasal symptoms. Patho-

\* Ricketts Lecture, 1964. See Bibliography.

† *A History of the Rockefeller Institute 1901-1953* (N.Y.: Rockefeller Inst. Press, 1964).

genicity of swine flu for mice was also established. Tests on both sides of the Atlantic showed that the swine and human viruses were antigenically related, though not identical. In cross-immunity experiments, only partial protection was produced by the heterologous virus.

Swine were found to be susceptible to infection by the human virus; this gave rise to filtrate disease unless the *Haemophilus* was present also. During 1937, sera were obtained from pigs at farms near two institutions where flu outbreaks were in progress: the results showed that the pigs too had become infected with the human viruses, though no adverse symptoms among them had been observed. These observations suggested that swine influenza, which had first been observed in the Midwest in 1918, might have originated from the transmission of the pandemic virus from man to pig. This idea was put forward independently by Laidlaw in Britain and by Shope. Remarkable confirmation came from studies of antibodies in people of different ages. Shope found, in 1936, that hardly any human sera from children aged twelve or less would neutralize the swine flu virus while many from older persons did so. This suggested that a virus antigenically related to swine flu had been present in the human population up to 1924 but not later. (One may reasonably suppose that the virus responsible for the 1918-1919 pandemic persisted for a few years after that catastrophe.) Work in several laboratories has confirmed these suggestions, and the relation of swine flu virus to the pandemic strain is generally accepted as being highly probable.

The discovery of the swine influenza virus and the bearing of the findings on human disease remain Shope's greatest contribution to knowledge. The next phase of his work, beginning in 1941, is much more controversial. His observations in the field had taught him that the disease was commonly absent during the summer but might break out explosively in October and November. Moreover this might happen, perhaps after the

onset of inclement weather, in several farms simultaneously. There was no question of direct transmission of virus from one farm to another; it seemed rather that virus had been seeded into the herds beforehand and then activated in many pigs at the same time. After pursuing other clues which proved unrewarding, Shope concluded that swine lung worms were acting as intermediate hosts. Ova laid by these worms are passed in the pigs' feces and taken up by earthworms in which the eggs hatch and undergo further stages in development. Pigs are fond of eating earthworms; the lungworm larvae are thus ingested and eventually reach the pigs' lungs, thus completing the cycle. Shope concluded that lungworms from flu-infected pigs would carry the virus in an inapparent or "masked" state throughout this cycle. On regaining a position in the lungs of fresh swine, the masked virus would not have its pathogenic properties restored until some stress to the pig had triggered something off; only after that did respiratory illness result. Shope had no difficulty in infesting earthworms with lungworms from flu-infected swine and in passing them back to fresh animals, which he called "prepared" swine. Disease was most readily provoked by repeated injections of these swine with cultures of *Haemophilus*: it could also be activated by exposure of the pigs to hard weather. Unfortunately the outcome of the experiments was irregular; success was obtained in only about half the attempts. Moreover, virus could never be demonstrated in lungworms by direct tests.

Opinions are much divided as to the validity of Shope's explanation of the facts. Some have accepted it as gospel, others have been wholly skeptical. The technique to test its truth has been beyond the reach of most workers: so few have attempted it. Those who have, have met varying success. I myself was unsuccessful: Shope gave me infected earthworms to take back to England, but there the attempted provocation did not lead to any disease.

Shope was wont to argue that had it not been for the fortunate existence of a suitable, available, intermediate host, swine flu could never have persisted in North America. On the other hand, I used to argue with him that neither the earthworm with which we were most concerned, a species of *Allolobophora*, nor the pig were native American animals and that I could not believe that a complex biological cycle involving three species could be evolved almost overnight.

One can now look at influenza in better perspective. It is now known that strains of influenza A virus infect man, pigs, horses, several other mammals, and many species of wild and domesticated birds. Only among swine in North America is there a suggestion that a complex cycle involving worms is concerned. Elsewhere, and particularly in man, outbreaks of influenza start mysteriously and explosively: there is, in general, no possibility that a cycle in worms plays any part. One must, I think, conclude that though swine flu virus may well persist in lungworms and earthworms in North America, it probably does so passively and is not of as great epidemiological importance as Shope supposed.

In 1930 Shope's attention was drawn to "mad itch," a violent, distressing, and fatal disease of cattle in the Midwest. He showed that it was caused by a virus transmissible to rabbits, and that it was endemic among pigs, in which it was comparatively harmless. Cattle contracted infection through contact with pigs. He finally proved the identity of mad itch with pseudorabies, a disease prevalent in parts of Europe. Later he studied another disease of pigs—swine pox—and showed that it could be, though it was not necessarily, transmitted through the agency of pig-lice. He also published evidence that hog cholera virus might persist, as swine flu virus appeared to do, in lungworms.

Shope's three most outstanding discoveries followed each other in rapid succession: swine influenza in 1931, the rabbit fibroma in 1932, and the rabbit papilloma in 1933.

The infectious fibroma, often referred to as the Shope



fibroma, was discovered on a shot cottontail rabbit (*Sylvilagus*). Minced material from this was inoculated into domestic rabbits (*Oryctolagus*) and readily produced growths, especially in young animals. Inoculation into the testis was most successful; intradermal and intraperitoneal injections gave less constant results. The growths consisted of proliferating fibroblasts; in the overlying epidermis eosinophilic granules were seen, though only in the cottontails. Shope emphasized that this was a tumor only in the broadest sense of "a local swelling consisting of a mass of new tissue."\* This was wise, since the tumors normally regressed. One persisted as long as seventy-seven days in a cottontail, but regressions occurred much earlier in domestic rabbits. It was soon shown that the growths had a filterable cause since an infectious agent passed a Berkefeld V filter. There was, however, no evidence of spread by contact. When infection was transferred, it was evident that the host's cells were being infected: it was not a question of transplanting a graft. Recovered rabbits were immune to further infection and developed neutralizing antibodies in their sera.

The character of the infection suggested to Shope a possible relationship to rabbit myxoma. This infection, of South American origin, causes local lesions in the native rabbits, another *Sylvilagus* species, but in domestic rabbits causes fatal disease. Shope found that rabbits recovered from his fibroma were largely resistant to the myxoma virus: they still developed local lesions, but almost all survived. Some measure of cross-immunity was also apparent in tests with antisera against the two viruses. The fibroma virus has been used subsequently as a practical method of immunizing rabbits against myxomatosis.

By analogy with myxomatosis it seems likely that the fibroma is mechanically transmitted by insect bites, but Shope's investigation of this in the field was never completed.

In 1936 Shope sent me some fibroma material, which I duly

\* *Journal of Experimental Medicine*, 56(1932):793. See Bibliography.

inoculated into rabbits' testes. Most surprisingly there appeared only acute inflammatory lesions instead of the expected proliferative changes. Moreover, many inoculated rabbits developed generalized pock-like lesions on their skins. This "inflammatory" strain was antigenically identical to the original one. Shope noted similar changes in one of his strains, and we collaborated in work that seemed to indicate that a mutation had occurred in the direction of greater virulence for rabbit cells.

Another development of work on the fibroma was the finding in several laboratories that various factors could cause the benign self-limited fibroma to become a generalized, persistent, or even fatal infection. These factors included the simultaneous injection of carcinogens or cortisone, application of X-rays, or the use of very young rabbits. The importance of work on the fibroma is its demonstration that the distinction between infection and neoplasia may be largely artificial: Shope's fibroma is one agent which bridges the gap.

Still more important in this connection is Shope's rabbit papilloma. Cottontail rabbits shot in Iowa and Kansas frequently have horns or warts on their skins. Shope found that material from these would readily produce warts on the skins of cottontail or tame rabbits when rubbed into the shaved and lightly scarified skin. The warts usually began to appear after six to twelve days: they might regress after a time or persist indefinitely as tall, often black, horns. The warts proved to be caused by a virus that gave rise to neutralizing antibodies: recovered animals were immune to reinfection. In cottontails the warts could be passed in series without difficulty, but the warts in domestic rabbits, even though well-developed, commonly failed to be transmitted to further animals. Shope devoted much attention to this matter: he did occasionally obtain successful serial transmissions in the tame rabbits, but failures were the rule. The important discovery was then made that the tame rabbit warts, though apparently virus-free, would lead to the production of specific neutralizing antibodies when injected

into rabbits intraperitoneally. The virus, or an essential part of it, was still there, perhaps in a masked form. This brought out the point that a virus might be the cause of a neoplastic condition, yet not be directly demonstrable. Critics of the work maintained that the difference between the wild and tame rabbits' warts was a purely quantitative one, but further work rendered this unlikely. Though many may be reluctant to believe in the "masked" swine flu virus in lung-worms, the "masked" papilloma virus seems to be genuine. Shope suggested that it might survive as infectious DNA, but since it gives rise to neutralizing antibodies, there must be more of it remaining than that.

The work gained a new dimension when it was found that in many tame rabbits the warts progressed and became carcinomatous. This change, though common in domestic rabbits, was rare in cottontails. Shope, at this time, was busy with many problems, so he generously gave the material to Francis Peyton Rous. What Rous did with the rabbit cancers during the next thirty years is a matter of history.

When the war came, there were fears that the enemy might seek to interfere with food production in North America by introducing the very infectious disease rinderpest into American cattle. Shope, attached for this purpose to the Army, was asked to take charge of a joint United States-Canadian project to produce an effective vaccine. Stringent precautions were necessary to prevent the escape of the infection, and laboratories were accordingly set up on Grosse Isle, a small island in the St. Lawrence River below the city of Quebec. Here Shope, with a staff of five other scientists, worked in strict isolation, and in the course of nineteen months produced an effective vaccine by growing and attenuating the virus in hens' eggs. This has since been used on a large scale in the field.

With this work completed, Shope asked to be transferred back to the Navy, which had been his original wartime assignment. T. M. Rivers was in charge of a U.S. Naval Medical Re-

search unit and, in 1944, got together a powerful team including Shope. There was little knowledge of what medical dangers might threaten men attacking islands in the Far East. When the invasion of Okinawa was planned, Shope was a member of a medical team that landed with the assault party in April 1945. A laboratory was established and was at times under fire. Fortunately the disease hazards were not found to be great, and before long the group was ordered to return to Guam. Even under war conditions Shope's inquiring mind sought fresh opportunities. He collected in the Pacific a number of molds, hoping to find one that would be of chemotherapeutic value. One of them, from Guam, grew on the cover of a photograph of his wife, Helen, and later this yielded an extract, which he called Helenine, having activity against several viruses *in vivo*. It was proved later that this was due to a nucleoprotein in it capable of stimulating interferon production.

Soon after the war, in 1947, fell a severe blow. Shope, essentially a country lover, had enjoyed being able to live near Princeton University on a small farm where he could keep a cow and poultry and grow vegetables. Then, with no previous warning to the staff, the Trustees of the Rockefeller Institute decided to close down their Princeton branch, offering the staff the opportunity to work in their main Institute in New York. Shope hated the idea of having to work in a city, especially as he needed facilities for work with large animals. So in 1949 he resigned and accepted a position as Assistant Director of the Merck Institute for Therapeutic Research in Rahway, New Jersey. Here he continued his work, chiefly on Helenine. But work within a commercial organization was quite foreign to his temperament, and in 1952 he returned to the Rockefeller Institute (now the Rockefeller University) in New York, living in an apartment across the street from the Institute but going back whenever possible for a weekend at his "gentleman's farm" near Princeton.

Because of his wide knowledge, common sense, integrity, and complete sanity Shope was a valued member of many committees, too many for his liking: at one time or another he served on no less than forty-five. Many of these were government or state committees, particularly those dealing with diseases of animals. Later he served on several of those concerned with cancer research.

Shope received many honors. He was elected to the American Philosophical Society (1944) and the National Academy of Sciences (1940). He received honorary degrees from the universities of Utrecht, Rutgers, Giessen, Chicago, Pennsylvania, Iowa, and Yale, as well as many prizes and awards including the U.S. Army Legion of Merit and the Albert Lasker award.

In the course of his work he became infected with two serious virus diseases, lymphocytic choriomeningitis and eastern equine encephalomyelitis, but in each case he made a good recovery. Some years before his death he underwent a major operation when a small abdominal cancer was found. For a long time there was every hope that it had been completely eradicated, but the hope was not realized, and he died on October 2, 1966. He is survived by his widow, three sons (Richard, Robert, and Thomas), a daughter (Nancy), and numerous grandchildren. The three sons are all following their father's footsteps in adding to medical and veterinary knowledge.

This account tells something of Shope's very great achievements. It is more difficult to give a picture of his personality. His was an unspoilt nature. He had simple tastes and above all a vivid sense of humor. He was fond of recounting anecdotes, and they became more remarkable, and rather less credible, with each time of telling. From the age of six his summer vacations were spent by Woman Lake, Minnesota, where he and his brother hunted and fished. He returned there again and again to one or another site by the lake. I like to remember him as he was during those happy days at Woman Lake.

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