THE WORM TURNED—ACTION AND REACTION*

DONALD L. AUGUSTINE

Harvard School of Public Health, Boston, Mass.

My reason for selecting a subject on worms for this address is that my professional career has been largely devoted to the study of parasitic worms, and I have always found these creatures interesting and at times exciting. It is, therefore, another instance of "Doing What Comes Naturally."

At what time man first attached any significance to the action of worms must be a matter of pure conjecture; it is quite unimportant. But at one time, somewhere along our ancestral trail, someone possessing that rare quality, curiosity, stopped long enough to watch a crawling creature; he probably poked at it, and also, probably to his astonishment, noted that the creature turned sharply against the poker. The observation provoked an idea: the proverb, "*The worm turned.*" Thus, a saying burst forth. It was pleasing, it spread, became commonplace and, let us say with all due credit to Theodor Storm, the author of that delightful novelette, "Immensee," it sprouted, it dropped from a cloud, floated over land like gossamer and was sung in a thousand places at the same time. It became a favorite epigram of poets and scribes.

You may well recall that Clifford, in Shakespeare's "Henry IV," cautions his gracious liege that, "The smallest worm will turn, being trodden on." And, Cervantes, being more than a little vexed over the publication of a second "Don Quixote" while he was preparing his own second part for press, notes in his foreword, "Bless me, Reader, gentle or simple, or whatever you may be, how impatiently by this time must you expect this Preface, supposing it to be nothing but revengeful Invectives against the Author of the second Don Quixote. But I must beg your pardon—though it be universally said, that even a Worm when trod upon, will turn again, yet I'm resolv'd for once to cross the Proverb." And again, Thomas Randolph in his entertaining "The Muse's Looking Glass" takes cognizance of the fact that,

> "Poor worms being trampled on turn tayle,
> As bidding battail to the feet of their opressors."

This observation was made in 1638. I do not hold that it is exactly the precursor to the discovery of dermal infection made 260 years later by Professor Looss.

Despite its great age, the phrase has never grown stale or hackneyed. I would remind you of its fresh appearance in Roger Lee's fascinating autobiography, "The Happy Life of a Doctor" which was published just two years ago.

"The worm turned" was very much of an old saw to me until one day it suddenly came to mind and it carried new significance; in fact, it had a very singular meaning. It occurred some time ago during one of our symposia on malaria. The speaker, who was reviewing the history of malaria, at the moment was dwelling on the origin of Manson's mosquito-malaria theory. The old saw burst upon me, for it was indeed the *turning of a worm* that prompted Manson's theory; it ushered in a new era in medicine, it was the beginning of modern tropical medicine. Reflecting for the moment, I ceased to follow the speaker. I sat there recalling some of the turnings of worms which had had direct and forceful influence on the development of tropical medicine and tropical public health. I assure you I had visions of actions and reactions.

Now, seemingly going somewhat astray, I am going to dwell briefly on a certain phase of physics, a phase of the subject which was of particular interest to all of us early in our scientific careers; in fact, much before we decided upon a scientific career, namely, Newton's third law of motion; "To every action there is an equal and opposite reaction." Objects which turn are objects in action. Although the action and the reaction are always equal, the action may be readily perceived but the reaction may not be noticeable. For example, when a person pushes his stalled automobile along the street, the force

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he applies against the automobile is equal to that applied against the pavement. The action is perceptible, but the reaction is not. Let the pusher put on roller skates and the reaction becomes immediately and decidedly apparent. In other words, the roller skates were added equipment which made visual perception of the reaction possible. Similarly, the reaction to the turning of a worm was not sensed until comparable *added equipment* was applied. In the present presentation, reaction will refer to man's understanding and appreciation of the worm's action, rather than to a direct reaction; namely, any pathologic physiology.

In all probability our parasitic worms in ancient times did as much turning as they do today; there was the same action on the part of the worm but the equipment for sensing any reaction was lacking. Essentially there was little or no reaction. It is true that the commoner, cosmopolitan helminths, *Ascaris lumbricoides*, *Enterobius vermicularis*, and the larger tapeworms were known. Primitive man as well as the medievalite must have been well aware of these creatures. They did not know how they got into the body, but they were fully cognizant of the way they left the body. To some, they were the obvious cause of their intestinal disorders, abdominal pain, while to others their presence was an indication of normal health and well being.

However, once it was assumed that these worms could cause pain, it was natural first to suspect, and later conclude, that worms caused pain and illness elsewhere in the body, particularly the most violent pain, the toothache. The symptom was the disease, as a rule, but in other cases the cause of the symptom was considered the disease. The patient had worms, the worms were the disease. Thus, action was observed, but the reaction was overlooked except by the physicians who prescribed remedies against the worms or the disease. The naturalist, the zoologist of the day, speculated on the question of the origin of worms. Further than this point, it mattered little if the worm turned, for to them, it looked much the same on both sides. This trend of thought remained unchanged until well into the 17th century.

Then came an abrupt and glorious awakening, a time of spiritual and intellectual uplift, an age of *individual* scientific endeavor and unbiased observations. As far as the worms were concerned, that bit of added equipment permitting accurate observation of action and reaction was introduced, namely Leeuwenhoek's simple lens of small size and with considerable curvature for close focus. The study of intestinal worms became the vocation and avocation of the naturalist. It became a specialty; the reaction became more apparent than the action and a new branch of zoology, helminthology, came into existence.

The present long list of helminthologists could rightly begin with Marcus Bloch, Johann August Goeze, and Peter Simon Pallas, whose years were from 1723 to 1811. Whether these gentlemen would have accepted such distinction is, I believe, a bit of a question for each is well known, if not better known, for contributions in other fields; two were physicians and the third was a theologian. But all had a common avocation; they were naturalists in the true sense of the word and probably would have preferred to remain in this category.

Even in the present day of specialization it is difficult, if not hazardous, to place a scientist in any definite category. He might disagree with your classification. For example, some years ago at an evening seminar the then recent studies on bird malaria were to be presented. The speaker was the late Dr. Samuel T. Darling. The chairman reviewed Dr. Darling's outstanding scientific contributions and introduced him as a protozoologist. I was looking at Dr. Darling and noticed that he shuddered a bit; then he rose to speak, beginning somewhat as follows, "Gentlemen, I have been introduced to you as a protozoologist. Urumph! This is indeed something new and strange to me. I always considered myself a pathologist—and I hope I shall be remembered as such."

During the 18th and 19th centuries helminthology was in its heyday, and there were helminthologists of that day: Küchenmeister, Herbst, Colbald, Steenstrup, van Beneden, and many others; and especially Leuckart, affectionately recognized at home as *Altmeister der Helminthologie* and acknowledged as the great leader by students in all nations. The apparent force of the reaction equalled that of the action. Thousands of animals were examined for their worm parasites and records were made. It was discovered that a worm does not look the same on both sides. Sex was revealed. The experimental method was successfully introduced into research, life histories were discovered and the widespread belief in the myths of necrogenesis and abigenesis became lost in oblivion.

I look upon the elucidation of the life-history of *Trichinella spiralis* as the first epochal contribution of helminthology to the medical sciences, particularly to the fields of epidemiology and public health. You will recall that this worm was first described in 1835. Twenty-five years later it was demonstrated that *T. spiralis* could cause fatal illness in man and that, almost immediately following this discovery, the disease in Germany was recognized in epidemic proportion with high mortality. In the meantime the parasite had been of keen interest to the helminthologists. Herbst demonstrated the transfer of the worm from one animal to another. Leuckart, Virchow, Küchenmeister and others, by careful feeding experiments with laboratory animals, had worked out its complete life cycle, and Leidy had discovered trichinae in the flesh of swine. Studies of the great epidemics in Germany clearly showed that the disease was of porcine origin and government action for control was applied.

Epidemiology, due to the early influence of Sydenham, reached a high state of development during the 18th and 19th centuries, in the hands of British epidemiologists. The epidemiological inquiries of the time were, however, mainly directed toward establishing the distribution of the epidemic in time and space, the historical and inductive methods of epidemiological research. The cause was unknown and the methods for control lacked scientific support. The investigation of the epidemic was often not begun until after its termination. Thus, the early studies on *Trichinella spiralis* ushered in a new method of epidemiological research, the *parasitological* method, for here is the first epidemic disease for which both cause and transmission were fully known and for which sound control measures were available at the time of the epidemic.

Likewise, the first endemic disease of which the agent, host, and environment were known was of helminth origin, namely echinococcosis. This knowledge was gained through the application of the parasitological method of research and it led to astonishingly effective means of control. Prophylactic measures against the disease were proposed in 1863 to the Icelandic Ministry of Health and these measures were rapidly put into action. Prior to this time the prevalence of echinococcosis in Iceland was astonishingly high. Following the application of control measures there was a remarkable and steady decline in the number of cases. Sanborn visited Iceland in the early 1920's. Later, in an address before the Institut Pasteur, Paris, Sanborn remarked, "Iceland has long been known as the classic land of hydatid disease, but nowadays echinococcosis has diminished in frequency as strikingly as yellow fever at Panama following the application of preventive measures based on true and precise etiological knowledge." Today there appears to be no echinococcosis in Iceland. These are examples, par excellence, of reactions to the "turning of a worm."

When Dubini, in 1838, discovered hookworms in the intestines of an Italian peasant, his reaction appears to have been scarcely more than a fleeting glance. Fifty years later hookworms were recognized as the cause of a violent epidemic of anemia, that of Saint Gotthard, and twenty-five years after this epidemic, hookworm disease was recognized as a major public health problem on every continent. Hookworm control was a potent force in the introduction, development and extension of public health services throughout the world, particularly influencing their development in rural areas.

From the very beginning, public health services were designed primarily for the improvement of the health and comfort of the city dweller and to protect the city from epidemic disease. Even the later developments following the advent of bacteriology, food sanitation, methods for tracing epidemics, laboratory diagnosis, the preparation of vaccines and vaccine prophylaxis, were to a large extent developments of bacteriological laboratories within the city and for urban populations. The countryside, from ancient times, was considered a healthy environment and a refuge in times of pestilence.

Very late in the year 1899 Bailey K. Ashford saw a worm turn; in fact he saw thousands of these particular worms turn. All were parasites recovered from rural Puerto Rican patients; the peasants, the *jibaro*, sick and so utterly miserable that, according to Ashford, they could not be more so. Ashford proved the parasites were hookworms and a cause of the malady which was rampant throughout the rural areas of the island.

Ashford's reaction was explosive; it was epochal. Following the formal announcement of his discovery, Ashford made a strong appeal that government action be taken to combat the existent conditions. I will not relate the steps in the development and extension of hookworm control to rural areas throughout the world. These are well known by all present. I will note only that wider health services to rural communities followed the hookworm campaign as their benefits were realized. It can be rightly said that the foundation of rural public health was laid when it was realized that hookworm disease was a reality and that it constituted a serious menace to rural health and prosperity. This discovery marked the awakening of health consciousness of rural areas; a definite reaction to the "Turning of a worm."

There were many 'side reactions', or should I say 'chain reactions' to the turning of the hookworm. Of these, I shall briefly mention only two which I hold to be of particular interest and significance. These were the development of anthelmintic medication and the introduction of parasitology into the curricula of our medical schools.

Late in the 19th century, when ancylostomiasis was recognized as the cause of the Saint Gotthard epidemic, the known vermifuges proved to be worthless. An eager and competitive search began immediately for an effective drug. Bozzolo, in 1879, found thymol to be highly effective. Its value was confirmed by others, and it became almost a universal remedy and the drug of choice for nearly thirty five years. The search for better anthelmintics was, and is, continuous. In 1921, Hall discovered carbon tetrachloride to be remarkably effective against hookworm infection and, in 1925, he announced the discovery of tetrachlorethylene as a new anthelmintic, believed to be safer and even more effective than carbon tetrachloride. It remains today as the drug of choice against hookworm infection.

It was the results of crude experiments in which hookworm larvae were subjected to various chemicals which led to the use of thymol as an anthelmintic. However, its value as an anthelmintic, as well as the value of other anthelmintics, was judged for many centuries mostly by clinical improvement and the passage of worms. Our knowledge of the value of carbon tetrachloride and tetrachlorethylene as anthelmintics came from carefully-planned studies with critical testing on experimental animals. Such critical testing of anthelmintics was first approximated in 1884 by Grassi and Calondruccio. The method was overlooked, or at least unused, until it was reintroduced in 1902 by Stiles, and later developed in the United States Bureau of Animal Industry under Ransom. Hall did not limit his studies on anthelmintics to animal experimentation. To gain information on the safety and subjective effects of tetrachlorethylene, Hall ingested the drug one day shortly after breakfast, which included liver and bacon, both probably contraindicated, drank milk later which is also contraindicated and indulged in smoking throughout the day. As I recall, Dr. Hall was a fairly heavy smoker. He reported that the only apparent effect of this self-medication was a complete relaxation of the muscles on retiring that night leading to an unusual dream of levitation. It seems very likely that Hall's report never reached the masses; no addiction to tetrachlorethylene has been noted among the thousands who have tasted this little-known euphoriant.

Prior to the turn of the present century, parasitology was primarily a field for academic graduate study. It seems to have been given very little, if any, attention in the medical schools. In 1891, Charles Wardell Stiles returned to the United States after a period of study in Europe, to enter government service in the U. S. Bureau of Animal Industry. He had received the Ph.D. degree from the University of Leipzig where he studied under the renowned and immortal helminthologist, Rudolf Leuckart. The following year Stiles was lecturing in parasitology before the medical students of Georgetown University, the Army Medical School and Johns Hopkins University. He later introduced the subject in Medical Schools of North Carolina, Georgia, and Louisiana. Hookworm bionomics and hookworm disease must have remained foremost with him from his Leipzig days, for in his lectures to these students he emphatically stressed the possible existence of hookworm disease in the United States and he cautioned his students that, if they found cases of anemia in man in the tropics or subtropics, the cause of which was not clear, they consider the possibility of hookworm disease, make a microscopic examination of the feces and look for eggs of the parasite. It is of interest to note that Bailey K. Ashford had attended Stiles' lectures both in the Georgetown Medical School and the Army Medical School.

It cannot be said, however, that ancylostomiasis was of primary, or even secondary, influence in bringing parasitology into the curricula of all of our medical schools. Certainly it was not at the Harvard Medical School. In this school such recognition was a sequel of Theobald Smith's course, "Comparative Etiology of Infectious Diseases," first offered during the second half year in 1898. The content of this course is not described in the school catalogue of that year, but the catalogue of the following year states that the course was a fourth-year elective, and limited to men qualified to do original research work. It consisted of lectures and demonstrations on the comparative etiology of infectious diseases, general principles underlying infection, and on public health problems arising from infectious diseases of animals.

In 1900 three optional courses were added to pathology, one of which was a course on the pathology of certain parasitic diseases, given by Theobald Smith. Parasitic worm diseases probably were included, but none is mentioned. In 1901 the content of this course is more clearly defined: it was a course of lectures and laboratory exercises on animal parasites, particularly protozoa, and the infections produced by them. The annual examination in pathology for the following year included for the first time a question on parasitology, namely, "Give the complete life-cycle of the blood-parasite of tropical malarial fever as now generally accepted." Some questions on parasitism in the annual examinations in pathology for the next few years were comprehensive and would require answers mentioning hookworms. But no direct, specific, question on ancylostomiasis appears until 1907 when the student was asked to give the biology and pathological action of *Uncinaria*. Therefore, it seems quite clear that the introduction of parasitology at the Harvard Medical School was not a reaction to a worm's action, but rather to that of a protozoan which was, I suspect, *Babesia bigemina* Smith and Kilborne, 1893.

From the foregoing, it would appear that the development of helminthology was a reaction to worms affecting human beings and animals. This is the impression all of us could have gained from our college courses in biology and very likely also from graduate studies in parasitology. This is a very one-sided impression and it is due to the fact that, although our texts on biology and parasitology expressly deal with the important parasites, the word 'important' invariably means important to *man* and *domesticated animals* and, particularly, 'important' to *man*. The helminths parasitizing plants are either ignored or are given the slightest attention. Yet these plant-inhabiting helminths are world-wide in distribution, they rank among the worst agricultural pests and their significance as limiting factors in crop production is unknown.

I should like to give a specific example: Thirty years ago on the Island of Bangka which lies off the east coast of Sumatra, hundreds of acres were devoted to the growing of black pepper. The economy of this island was based on this crop. Today, due to a particular burrowing helminth, the pepper industry on this island has been wiped out. This same worm parasitizes citrus; it has already affected 8,000 acres of citrus in this, the State of Florida.

The plant-inhabiting helminths are all nematodes and include both obligatory and facultative parasites. Despite the fact that the first species was discovered more than a hundred years before the discovery of *Trichinella spiralis* was announced, and that its life-history stages and pathogenicity, *i.e.*, gall formation, were known almost a hundred years before trichiniasis was recognized as a disease, the plant nematodes interested but few of the early helminthologists and remained neglected until fairly recent times. Among the pioneers I would mention Needham of England, Kühn and Steinbuck of Germany and Dovaine and Chatin of France.

In 1907 a most remarkable man joined the United States Department of Agriculture as 'Agriculture Technologist'. He was enthusiastic, visionary, mathematical, and possessed of keen and rare sense of humor. It is rightly said of this man that he embodied all that is meant by a "scientist." He was Nathan Augustus Cobb; Nay Cobb to his close associates. Cobb's early fields of interest were in standardization of cotton types and free-living and plant nematodes. Under him the study of plant nematodes became a distinct and separate branch of helminthology, the study of nemas, or nematology; names introduced by Cobb, from which there were numerous derivations: "nematologist", "nematize", "nematosis", "nematicide." Cobb became 'Senior Nematologist' in 1924 and 'Principal Nematologist' in 1928. The category 'Nematology' was expressly created for Nathan Cobb, its meaning being restricted to studies on plant-insect-inhabiting and free-living nematodes.

Nematology, unfortunately, is still a much underdeveloped science, but the reaction to nemas is constantly gaining force. In 1950 the only agencies in the United States dealing exclusively with nemas were the Division of Nematology in the United States Department of Agriculture and the then-newly-established unit at the College of Agriculture and the Agriculture Experiment Station of the University of California. Today, less than 9 years later, there have appeared departments, sections, or currently-given courses presided over by trained phytonematologists (an even newer category) in the universities or land grant colleges of Alabama, California, Florida, Maryland, New York, North Carolina and Wisconsin.

I have to a large extent drawn attention to the actions and reactions of worms of earlier years. I should now like to consider briefly the nature of these forces today; first the magnitude and then the variability; whether the forces are static, and if not static, what is the direction or, in other words, what is the trend.

To appraise the magnitude, let us examine the record, namely, "Helminthological Abstracts." This exceptionally valuable source of information on all the many and varied applications of helminthology began publishing in 1932. In that year Volume I contained abstracts from 268 periodicals; 776 authors had published 873 papers. Volume V contained abstracts from 458 periodicals; 1,199 authors published 1,346 papers. Except for the war years there were steady expansion, more periodicals, more authors, more publications. Volume XX contains abstracts from 696 periodicals; 2,113 authors published 2,067 contributions.

I shall now point out the course helminthology has taken as it is reflected in the publications in our own Journals. First, let us turn to Volume XII, 1932, of the American Journal of Tropical Medicine; this is, as you may recall, the year Helminthological Abstracts made its appearance. A total of 39 papers were published, three of which were on helminthiases, namely, one on skin hypersensitiveness to hookworm antigen, one on complications of filariasis and elephantiasis and one on the treatment of intestinal parasitism by transduodenal irrigation with hot physiological salt solution. This reflects the pattern of the Journal, as far as publication in the field of helminthology is concerned, from Volume I, 1921, to Volume XXIII, 1943. Papers on helminthological subjects made up approximately 10 per cent of our total scientific contributions.

A change, a concentration on certain phases of helminthology, begins with Volume XXIV, 1944. In this volume only six of the 57 contributions deal with helminths, but five of these papers have to do with filariasis; and two of these announce filariasis in American troops serving in the South Pacific area. Volume XXV, 1945, announces hyperendemicity of schistosomiasis on Leyte Island, another theater of the war. Eighteen, or more than 22 per cent, of the contributions deal with helminthiases; of these, 12 have to do with filariasis and five with schistosomiasis. Schistosomiasis and filariasis continue to be foremost subjects in The American Journal of Tropical Medicine and Hygiene. Volume V of our new Journal published a total of 125 contributions of which 44, or 35 per cent, deal with helminth infections. Twenty-two of these papers are on schistosomiasis and four are on filariasis. The same pattern obtains today. Number five of Volume VII, which has just appeared, contains fewer original contributions, 17, but three of these deal with schistosomiasis, two with filariasis and three are concerned with insect vectors of filariasis. The emphasis remains on host-parasite relationships, epidemiology and control.

World War II is responsible for this trend; concentration and markedly increasing activity concerning two tropical diseases which heretofore, in this country, were matters of special interest to only a relatively few research workers, physicians connected with medical missions or with industrial firms operating in the tropics. World War II ushered in a sudden change. It was somewhat of a rude awakening to the fact that the whole world had shrunk, that our public health problems were no longer limited to continental U.S.A., and that the solution of the health problems of the warm climates, particularly health problems of parasitic origin, are of primary importance. From the outset the reaction was international. Never has there been greater impetus to mobilize the resources of the Free World to combat and abate disease and to improve living conditions, not just in the Tropics, but in all parts of the world. The aim has been towards international friendship and peace, international cooperation "For survival instead of destruction." Surely, the worm turned; it keeps on turning; there is action and there is reaction. The reaction is clearly visible and distinct; it is definitely equal and opposite to the action.

In closing, I want to express my deep appreciation to those who gave me the privilege of serving as President of our Society. For me it has been an honor, a very singular honor and pleasure.