EDITORIAL COMMENT

This issue of PHOENIX is concerned with schistosomiasis—often called bilharziasis—a parasitic disease caused by a small flatworm that uses human beings as a final or definitive host. Estimates of the number of people afflicted with schistosomiasis range from a low of 114 million to a high of 200 million. These infested people live principally in agricultural communities in Asia, Africa, and South America, where they come in constant contact with the streams and irrigation canals that serve as the home of the worm’s intermediate host—a snail. In many areas, particularly Asia, schistosomiasis is also a disease of animals, thus adding detrimental economic effects to its human toll. Because of the growing number of countries in which the disease is known to exist, because of the extension of the snail habitats in these countries and the growing number of infested people, schistosomiasis has become the leading candidate for the dubious honor of being the world’s worst health problem.

The interest of the Phoenix Project in schistosomiasis stems from a research program supported by the Project and conducted in the Phoenix Memorial Laboratory. This program is using radiation from a cobalt-60 source in an attempt to create a vaccine that will provide immunity to the disease. The existence of the program demonstrates that there is an unlimited value in having people trained in radiation technology available to apply the techniques of this area to a problem unrelated to nuclear energy, electric power, bombs, or cancer. It is a role in which radiation becomes simply a tool, not a panacea. And as a tool, it is just one of many with which to approach the problem. When radiation wanders away from physics or nuclear engineering the potential contribution that it can make to benefit mankind, remains great, as it does in the research on schistosomiasis. To realize just how great one must understand the history of schistosomiasis, its effects on people, its scope, and the problems that have been raised in the attempt to control the disease. It is to this purpose that this issue is directed, with the realization that any conclusions about the significance of radiation research on schistosomiasis is equally true of ‘non-radiation’ research on schistosomiasis.

A study of this parasitic disease carries with it a sobering lesson about the nature of man’s ability to harness science and technology to solve his problems. Schistosomiasis has existed almost as long as man has recorded history. Yet, in 1961, the prophylactic methods for controlling the disease are ineffective, the known methods of curing the disease are almost as bad as the disease itself, and there is no known way of making people immune to the disease. There is an extensive amount of knowledge about schistosomiasis that did not exist when it was first recorded thousands of years ago—but there has not been a comparable improvement in our ability to deal with the disease. In fact, schistosomiasis has become a byproduct of Progress—as modern techniques of irrigation are introduced into agricultural communities where the disease exists, the disease spreads. Ironically, there was a better natural balance between man and the schistosome worm under primitive technology.

On the credit side of the record, however, is the fact that all the progress in diagnosing the disease, in understanding its cause and the manner in which it is spread, in partially treating it, and in partially preventing it, occurred in the last 100 years. Further, most of the promising research, which might at any time provide the answers to schistosomiasis control, has been done in the years since World War II, a small capsule of time compared to the centuries during which the disease is known to have existed. The two projects reported in this issue of PHOENIX represent such progress.

They are only two of the many methods by which man seeks to control schistosomiasis. Another occurs at the research divisions of pharmaceutical companies throughout the world (Parke Davis, Eli Lilly, Ciba, Lederle, are just a few) where chemicals are being tested on schistosome-infested animals in an attempt to find a drug that will kill the worm more effectively than present treatments. The reports of this work are encouraging. A few drugs have already passed the animal experimental stage and are being used in tests on humans in endemic areas.

Schistosomiasis and the problems it brings with it are so complex that no one scientific approach, be it radiation, pathology, chemistry, zoology and no lone solution, be it snail control, vaccination or cure, is likely to provide the total answer. Rather a combination of many disciplines and of many solutions will need to be brought together before man can conquer the microscopic parasite that has so conveniently lived off him for centuries. The gnawing persistency of this worm is an unhealthy reminder that not all the progress of science lies in some future world of technological space marvels, but that important goals remain to be reached on existing human problems, and rather earthy ones at that.
On May 19, 1798, to the tune of martial music, a French squadron of four hundred transport vessels, guarded by a convoy of ninety-three ships of war, set sail in Toulon Road. In the flagship l’Orient were Napoleon Bonaparte, the principal members of the Commission of Science and Art and the chief physicians of the Grand Army. In the transport ships were 30,000 soldiers and 108 surgeons, making a ratio of one physician for every 278 soldiers, a figure expressing a solicitude about the health of the Grand Army that was to be borne out in the coming expedition. On June 30th, the fleet lay to before Alexandria, having stopped briefly on the way to conquer the island of Malta.

At Alexandria, ten thousand soldiers disembarked, marched to the walls of the city and carried them by assault after several hours of fighting. Only two hundred and fifty Frenchmen were wounded in this initial battle, a loss that was not considered serious. In treating these casualties, the surgeons, according to the Inspector General of the Medical Staff, D. J. Larrey, were aided by the “favourable influence of this climate on wounds.” “The short time in which the wounded were healed,” Larrey wrote in his Memoirs of Military Surgery and Campaigns of the French Armies, “was truly astonishing.” Napoleon’s conquest of Egypt, it has always been conceded, began auspiciously. The massed strength of the French Army, seemingly aided by the beneficient nature of the country it was invading, was ready to seize victory.

During the next three years the French armies marched as far north as Syria, as far south as the Nubian Desert. At the end of this time, the remnants collected at Alexandria, their fleet no longer existent, Napoleon back in France, a British army encircling them. Larrey summarized their plight in his Memoirs. “We were now surrounded on all sides and closely besieged. Our hospitals were crowded with the sick and the wounded. This unfortunate situation, the sickness of the troops, the want of many articles of prime necessity, as well as other motives unknown to me, induced the commanders of the two armies to open negotiations.” The surrender of the French army was signed on August 31, 1801.

A French historian, Jean Joseph Ader, writing some twenty years later, concluded his Histoire de L’Expedition D’Egypte et de Syrie, with a list of the obstacles that the French Army had to overcome in its attempted conquest of the Middle East. First are the “extraordinary events,” then “the beatings of the climate,” “the intrepid troops of the Beys,” “the war-like inhabitants of the desert,” and finally “the prejudices of religion” and “social customs.” Ader omits only the diseases, spawned in Egypt, with which the French soldiers were soon heavily afflicted.

These, however, are detailed in Larrey’s Memoirs: plague, scurvey, ophthalmia, yellow fever, hepatitis, leprosy, elephantiasis, the bites of scorpions, the attachment of leeches to the passages of the throat and nose. His book is an impressive record of the diseases peculiar to armies, semitropical climates, and the 18th century. In addition, unknown to Larrey, there was at least one other disease that had helped destroy the French expedition. Two years after the
Two schistosome worms recovered from an infested mouse. The male worm is holding the ends of the longer and more slender female in a ventral groove. Actual length of the male worm is about 8 millimeters, of the female worm, about 12 millimeters.

surrender at Alexandria, a physician who had been assigned to a division campaigning in Upper Egypt reported on “a most stubborn hematuria,” that had been prevalent among the troops. Writing in the Journal General de Medicine de Chirurgie et de Pharmacie in 1803, Dr. A. J. Renoult attributed this disease to the same climate that had seemed so beneficial when the invasion was first begun.

“In this country, as in all others, a mild and continuous perspiration is an absolute necessity for the conservation of health,” Renoult wrote. “I have had occasion to observe that the great abundance of sweat gives rise to some illnesses, even to some grave ones. Such a case, for example, is a most stubborn hematuria which manifested itself among the soldiers of the French Army during the conquest of Upper Egypt. The disease appeared to affect most particularly the cavaliers, not sparing even the horses. The ravages carried themselves principally among the youngest. . . . the continual and very abundant sweats diminish singularly the quantity of the urine, the latter becoming thick, bloody. Often even, the last drops are pure blood. The sickness gives sharp pains in the region of the bladder . . . the last contractions of the bladder are accompanied with the most lively and piercing pains . . . .”

In Larrey’s Memoirs, this same hematuria is frequently reported as a symptom or effect of hepatitis, yellow fever, and the plague. Because of the strong possibility that many of these cases were really the disease Renoult isolated, Larrey’s Memoirs together with Renoult’s report are considered the beginning of the modern history of a disease that has replaced malaria as the chief public health problem in many underdeveloped nations. Known in Africa as Bilharziasis and in the rest of the world as Schistosomiasis, this disease is currently carried by more than 114 million people in the semitropical and tropical regions of the world. The modern discovery of Bilharziasis is at least one answer that can be given to the rhetorical question of the historian Ader, who after describing the Egyptian campaign as one “that ended beautiful in its sadness, admirable in its aspirations,” asked “What remains of this brilliant conquest?”

The cause of Bilharziasis or Schistosomiasis is a parasite, a member of the flatworm or trematode family, commonly called a blood fluke. Though considered an animal of a low order of development—it has a meager nervous system and no blood system—the fluke has one of the most intricate and highly specialized reproductive cycles. The fluke must develop through several forms in several media before it finds a final host and grows into adulthood. For the flatworm that causes Bilharziasis, the final host, unfortunately, is man. Within the human, the worm mates and lays millions of eggs, many of which pass out of the body but many of which become embedded within various tissues of the body, disrupting their function, and causing Bilharziasis. Three varieties of the disease are known to exist, each caused by a different species of the worm: Schistosoma haematobium in Africa and Anterior Asia; Schistosoma mansoni in Africa, South America, and the West Indies; and Schistosoma japonicum in Asia.

The symptoms of Bilharziasis haematobium, the variety the French soldiers contracted, combine at the onset of the disease to produce a general malaise.
There is an irritating cough, a skin rash, headache, loss of appetite, aches and pains, fever and difficulty in breathing. In the acute stage, the symptoms increase in severity. Nausea sets in along with diarrhea, dysentery, and most specifically blood in the urine. In the disease's chronic stage, the liver shrinks, the spleen becomes enlarged, the abdomen bloated while the rest of the body becomes emaciated. The internal tissues in which the eggs have encysted thicken and become fibrous. Cancerous growths often result as well as lesions of the lungs and heart and even infections of the brain. Eventually the disease kills, if not directly, by drastically shortening the life span. The other two varieties of the disease, being intestinal, are not distinguished by hematuria. The other symptoms remain the same.

People with chronic Bilharziasis are often described as lethargic and understandably so. The effect of the disease on a nation's productivity becomes apparent with the fact that in rural areas where Bilharziasis is endemic, infection is close to 100%. It is estimated that in Egypt alone there are approximately nine million cases, almost 40% of the population.

Normally, as one authority on parasites has pointed out, “A parasite's existence is usually an elaborate compromise between extracting sufficient nourishment to maintain and propagate itself and not impairing too much the vitality or reducing the numbers of its host, which is providing it with a home and a free ride.” The blood fluke that causes Bilharziasis, while extracting a high price, does not run counter to this pattern. Though it more often than not kills its intermediate host, a snail, and drastically impairs its main host, man, the fluke has ensured the survival of its species over forty centuries of recorded history, living off both its snail and human hosts without eradicating either.

The antiquity of Bilharziasis was first suggested by the discovery of several Egyptian Medical Papyri that describe the illnesses of the people of the Nile Valley and the remedies used in treating them. The principal evidence is in the Papyrus Ebers, found near Luxor about 1870. Though written in hieratic script dating from about 1550 B.C., the Papyrus Ebers, as evidenced by the textual references to early Egyptian Kings such as Usaphias of the First Dynasty, contains remedies as old as 3000 B.C. In the Papyrus Ebers, ailments are usually designated by simple, sharp descriptions—"fever," "burning in the eyes," "stiffness in the limbs,"—and are followed by a prescription or a course of treatment. Again and again hematuria is recorded in the Papyrus, each time followed by a different remedy and often accompanied by a diagnosis. A typical entry reads, "Another remedy to expel magic in the belly and blood in the urine, caused by a god or a dead man in the belly of a man." The prescription that follows calls for a combination of herbs—some known and some unknown—"made into powder, put into beer and drunk before going to bed."

A wiser and more fatalistic diagnosis in the Papyrus Ebers connects the hematuria to worms, though in a causal relationship opposite to what we know to be true today. "Another excellent remedy among those prepared for the belly," an ancient physician wrote: "'isw/s3m's' are ground fine, boiled with honey and eaten by a man in whose belly there are 'hrw'-worms. It is blood in the urine that produces them and they are not killed by any remedy."

The possibility that none of these early prescriptions were meant to cure the disease now known as Schistosomiasis or Bilharziasis existed until 1908. In that year, Sir Marc Ruffer, Professor of Bacteriology in the Cairo Medical School, proved conclusively that the ancient Egyptians suffered from Bilharziasis. Ruffer, who founded the discipline of "paleopathology"—the medical examination of prehistoric bodies—had obtained several mummies from excavations in the Nubia made prior to the flooding of the area by the erection of the first Asswan dam. After examining his desiccated patients he reported to the British Medical Journal that "in the kidneys of two mummies of the twentieth dynasty (1200—1085 B.C.), I have demonstrated in microscopic sections a large number of calcified eggs of Bilharzia haematobia, situated for the most part among the straight tubules. Although calcified, these eggs are easily recognizable and cannot be mistaken for anything else."

Several thousand years after these Egyptian mummies were interred, the French Army surgeons had little more to offer their patients than had the Egyptian physicians who entered their remedies in the Papyrus Ebers. "In treatment of this disease," Renoult wrote in his report "I obtained some momentary successes by the use of abundant liquids and above all, some rest. I have noticed that the vapour baths, much in use in the country, had no happy results, doubtless because of the abundant
perspiration which determined the disease; the river baths appeared no more useful. The use of these means during a month sufficed to show the symptoms of this disease disappearing. But as soon as the subject was obliged to take up his exercises again—and above all horseback riding—the urine became less copious and more acrid, giving place to new pains, to a feeling of sluggishness in the region of the bladder; and the hematuria reappeared. Carrying the patients on litters on the back of the camels which followed all the movements of the army, appeared to me to aggravate the disease more, as a new irritating cause."

"It is thus," Renoult concluded in much the same mood as the physicians of the Papyrus Ebers, "that a long sojourn in these countries has given this disease time to get a good hold, a hold of such stubbornness that after two or three years, the sick returned to Europe and uselessly sought cures. In a great number, the hematuria became so rebellious that it left them only the sad perspective of an old age filled with suffering."

Not until a century later, in 1918, was a cure for Bilharziasis discovered—the highly toxic, potassium antimony tartrate—a cure that could be as grave as the illness and which proved subsequently to have such serious drawbacks that its efficacy was limited. Between the modern rediscovery of the disease by the French army physicians and the discovery of a cure the cause had to be known. This did not occur until 1851, when Dr. Theodore Bilharz, a German, who was Professor of Anatomy at the Medical School in Cairo, wrote several letters to his mentor, C. T. von Siebold, announcing that he had found a new flatworm in the portal vein of a cadaver.

"After my attention was turned to the liver and the connecting vessels," Bilharz wrote, "I soon discovered in the portal vein an abundance of long white worms, which, with my naked eyes, I took to be round worms; but recognized as something new. A look in the microscope enabled me to distinguish a magnificent flatworm with one flat body wrapped around another . . ."

An exchange of questions from von Siebold and answers from Bilharz together with new discoveries, succeeded in identifying the male and female worm, the thorned eggs of the worm, and, most important, succeeded in establishing a theoretical connection between the worms and disease symptoms. This last discovery took place in 1852, when Bilharz, performing a post-mortem on a boy who had supposedly died of meningitis, found an abundance of the worms he had discovered the year before.

Von Siebold honored his pupil's discovery by naming the worm Distomum Haematobium Bilharzi. Unfortunately, in 1858, a Dr. Weinland of Harvard University renamed the worm Schistosoma, (meaning split body) and began a controversy that has continued to this day. On the occasion of the 100th anniversary of Bilharz's discovery, one of the leading modern authorities on the disease, Dr. C. H. Barlow, listed his objections to the use of the name Schistosomiasis. "The body of the male worm . . . only appears split or divided because it is folded over to form a channel or groove in which the female worm lies throughout its life. It is a flat worm like all the other fluke worms, but folded over. The correct name should combine the meaning, "folded" with "body." The worm was called haematobia from the fact that it produces blood in the urine. Today, the disease is known as Schistosomiasis in the Far East and in South America, and as Bilharziasis all over Africa. This confused state of affairs needs clearing up."

The semantic problem, however confusing, did not prevent diagnosis of the disease and a growing awareness of its widespread nature. Using one name or another, Bilharziasis or Schistosomiasis, physicians began to steadily report on the incidence of the disease.

When Bilharz found his new flatworm, the general life pattern of the trematode was known. In 1817, the resemblance between cercariae, (microscopic wormlike forms that have forked tails), and adult flukes had led to the assumption that cercariae were the larval forms of the flatworm. When in 1818, cercariae were observed emerging from snails, the mollusk was identified as a likely intermediate host. By 1851, it was believed that eggs from adult worms found their way into the snail, developed into cercariae that found their way into man, developed into the adult worm and produced eggs. When Bilharz connected a particular flatworm to the hematuria that had been observed in Egypt, the obvious task was to find the specific animal, most likely a snail, and the specific species of animal that served as the intermediate host for this new worm. If this were known, the manner in which the disease was contracted by humans would also be known.

Still, the early progress toward finding an intermediate host was mostly conjecture. In 1854, a para-
sitologist advanced the idea that the young Bilharzia "existed in the waters of the Nile," that same river that the French troops had found such a source of relief from the heat and thirst of Egypt.

The first person to experiment in the areas where the disease was prevalent was an Italian helminthologist, Prospero Sonsino. He, too, was unable to find the snail that was theoretically suspected to serve as an intermediate host. In 1893, Sonsino, explained his failure by writing that the intermediate host was not a snail but a microscopic crustacean or shell-fish. He concluded that the larva was transferred with the crustacean in drinking water to the human stomach where it eventually penetrated the intestinal walls and arrived in the portal veins. Sonsino was certain that a few simple precautions would prevent the disease. "Filtration, even rough filtration through linen," he wrote, "will afford complete immunity." Fortunately for Sonsino, he did not attempt to test his theory himself and the following year, safely retracted his conclusions.

This failure to discover the specific host for the Bilharzia worm led to the adoption by a renowned parasitologist, Looss, of a theory that there was no intermediate host. "All attempts made by former authors to discover an intermediate host in which this development is gone through have failed, and so have my own efforts," Looss wrote, "I have examined hundreds of specimens of all the mollusks common in the Nile Valley without finding any sporocyst [an intermediate form in the life cycle of the flat worm] which might have been brought into relation with the Bilharzia worms . . . . I am thus forced to the conviction that man himself acts as an intermediary host."

Looss' theory became a dominant one, opposed by very few of the many people doing research on Bilharziasis. The theory stood until several groups of Japanese doctors demonstrated the specific life cycle for the Asiatic variety, *S. japonicum*.

The Japanese work first came to world attention in 1904 when Dr. D. F. Katsurada reported the results of his research on a disease endemic in the provinces of Saga, Yamanashi and Hiroshima. The chief symptoms, as he described them, were enlargement of the liver and spleen, morbid appetite, diarrhea, fever, and anemia. "A certain number of the patients," he wrote, "died of extreme weakness."

The only clues to the cause of the disease were numerous eggs of an unknown parasite that were found in cadavers. These eggs looked like those of *S. haematobium*, though they lacked the characteristic thorn or spine. Dr. Katsurada noticed the similarity and conjectured that the disease was caused by a trematode. He was successful in his attempts to find such a worm in cats and dogs who were infested with the eggs. Because the worm resembled the Schistosome worm—the female lying within the folded body of the male—Katsurada named the trematode *Schistosoma japonicum*. When the worm was found in a human body by another Japanese, Dr. Fujinami, Katsurada's diagnosis seemed correct.

Four years later, Dr. Fujinami, participated in one of three separate experiments that successfully found the specific species of snail that served as the intermediate host for the Asiatic variety of Bilharzia. An English Army Physician, R. T. Leiper, reportedly,
was in Japan at the time and was shown the Japanese work. Leiper returned to Egypt to prove that the life cycles for *S. haematobium* and *S. mansoni* were similar to that of *S. japonicum*, that a snail and not man served as the intermediate host. C. H. Barlow has reported on the combination of fortune and knowledge that aided Leiper.

"When [Leiper] first arrived in Egypt, he looked long but could not find the snails involved in this country, nor did he find the fork-tailed larvae in the water. It was the wrong time of the year and it was only by a fluke (pardon the pun) that he found it at all."

"He fell ill with scarlet fever and stayed in the hospital for some time. When he finally came out, he tried again. It was then the right season and he found the two species of snails which were shedding cercariae, the fork-tailed infective larvae which are able to enter man."

Barlow’s seasonal references are based on the fact that cercariae begin to emerge from the snails in the spring—a fact not known during the early research but one which was most likely responsible for the failure of the early investigators to find the proper snail. Recent data from a World Health Organization Project on snail eradication has shown that the middle of May is the breaking point. Before this time the snails show no evidence of infection. After the middle of May and until winter the cercariae appear in large numbers. This same study revealed another factor that hindered the early discovery of the snail host—that only 1% of the snails carry the parasite. This small percentage, however, is a large number because of the millions of snails that exist in even a small area.

Leiper, in his own extensive reports on his research, does not mention the personal illness that aided his discovery, though he likes to point out the ironic fact of history that the village at which he conducted his research, El Marg, north of Cairo, was the scene of one of the battles between the French and the Egyptians in Napoleon’s campaign.

El Marg was an agricultural village surrounded by cotton fields and date palm groves. The water supply was a small canal, part of the Nile River irrigation system, which cut across the village, forming a shallow pool in the central square. Pictures taken by Leiper show the children of El Marg drawing drinking water from the canal, the women washing clothes in the canal, and the men standing in it. The canal was also the sewer system of the village and because of the practices of the Moslem religion which call for ablutions and because of the custom which calls for washing after excretion and urination, it was frequently visited.

At the time Leiper began his work, there were no records of Bilharziasis occurring in El Marg. His first preliminary examination of 54 boys in two village schools showed that 49 of them carried the eggs of Bilharzia.

During the Spring canal rotation, when the water in the canal was stopped and the bottom exposed, Leiper collected all the species of snails he could find in the canal. There were fifteen separate species, each of which was examined for cercariae and for earlier developmental forms of the Bilharziasis worm. Bilharzia cercariae were found in four species, of which the most highly infected were the species *Planorbis* and *Bulinus*. These two snails were found wherever the canal coursed through the village.

Leiper then conducted a series of experiments in which he immersed a calf, a lamb, mice, rats, geese, ducks, chickens, crows, and wagtails in water containing a large number of living cercariae. Positive
infection was obtained in rats and mice that subse-
quently died from blockage of their veins. Further
experiments with monkeys conclusively demon-
strated that the cercariae could enter the body any-
where they came in contact with it, either through
bathing or drinking.

Leiper’s work concluded one stage in the history
of Bilharziasis. The particular intermediate hosts for
the three types of the disease had been identified,
the life cycle definitely established, and the means
of infection demonstrated. Direct physical contact of
any sort with the waters in which the necessary
species of snail lived exposed a person to certain in-
fec tion and the opportunity to serve as a final host
to the parasitic worm.

The life cycle of the Bilharzia worm begins with
the adult male and female lying together, the male
wrapped about the female. The female lays chains
of small bead-like eggs, containing larvae, in the
mesenteric or pelvic veins of the human. These eggs
work their way into the bladder or intestines and
are passed out of the body with the urine or feces.
In warm water, within one minute to sixteen hours,
the egg hatches into a miracidium, a small larval
form with hair-like projections that enable it to move
through water. The miracidia swim about seeking the
particular species of snail that they need in order to
continue development. They have no more than 24
hours in which to find one. When the miracidia ar-
rive near such a snail they become excited, dart for
the snail and attach themselves to the soft tissue of
the head or foot or tentacles. Once attached, they
bore into the snail and migrate to the digestive
gland. There they grow into a sporocyst, a hollow
sac-like body with germ cells on the outer wall. The
sporocyst buds off a number of secondary sporocysts
similar to itself. After a time, each secondary sporo-
cyst migrates to the snail’s liver where it produces
the fork-tailed cercariae. The cercariae break out
of the sporocyst, leave the snail and swim about in
water. The cycle from egg to cercaria varies from
2–12 weeks. Once the cercariae leave the snail they
have about 24 to 36 hours to find a human host be-
fore they die. If they find one, they fasten them-

 selves to the skin by means of suckers, shake off
their tails, and in about 15 minutes pass through
the skin into the blood vessels. They then migrate
to the liver where they become adult males and fe-
males. From the liver they migrate to the veins of
the bladder or intestines where they lay eggs, and
the cycle is ready to start again.

The multiplication that takes place during the life
cycle is fantastically high. Each egg produces one
miracidium; each miracidium produces one sporo-
cyst; each sporocyst produces about 30 secondary
sporocysts each of which in turn produces about 40
cercariae. Ultimately each egg is responsible for ap-
proximately 1200 cercariae, each of which develops
into one adult. The multiplication through egg pro-
duction is even higher than in the previous stages of
the life cycle. Dr. C. H. Barlow, who infected himself
with several hundred cercariae, passed hundreds of
thousands of eggs—as many as 30,000 in a day.
Barlow’s case, contracted in Cairo in 1944, has
provided the most detailed description of the effects
of the disease and the effects of the cure. The rea-
sons he gives for subjecting himself to the disease
is that he wished to bring eggs into the United States
in order to determine whether any species of snail
native in this country could act as an intermediate
host. While this may seem a difficult approach, it
should be noted that in 1920, Barlow, for similar
reasons, had infested himself with eggs of another
parasite Fasciolopsis buski. This previous experience
The parasitic schistosome worms live in the human abdominal organs. Their eggs, passed into water habitats, hatch into miracidia. The miracidia enter snails and develop into sporocysts that produce fork-tailed cercariae. The cercariae leave the snails, attach themselves to humans and bore through the skin and into the blood vessels. In time, they migrate to the liver and grow to adulthood. The photographs, taken in Puerto Rico, show an infected canal, children playing in an infected stream, and two boys with Schistosomiasis. The boy on the right suffered from malnutrition which increased the severity of the disease.
at self-infection had not proved detrimental. He conducted his experiments and cured himself of the disease. Bilharziasis, however, was to prove a more difficult experience.

At the time Barlow started his self-experiment, he was 67 years old, weighed 176 lbs., and described himself as being in vigorous health. On May 31, 1944, he applied 8 cercariae of S. haematobium to his left forearm. On June 1, he applied 8 more to the umbilical region. On June 14, he applied a dish of water containing cercariae to the right side of his stomach. On the following day, 147 small red spots were counted in this area, and were considered to be the minimum number of cercariae that penetrated the skin. On June 21, a second application of cercariae resulted in at least 61 penetrations of the left side of the stomach. On July 4, Barlow flew to the United States.

No symptoms appeared until 76 days after the principal exposure, when his body temperature rose to 99.5° F. in the late evening with a fall to below 98.6° F. the next morning, accompanied by slight sweating. Daily fever continued for several weeks without significant increase in severity. The first eggs of the Bilharzia were found in seminal fluid on the 78th day. On the 106th day, eggs were found in his urine.

For the next 3½ months, eggs appeared in the seminal fluid, feces and urine in increasing numbers. In this period the physical symptoms became severe. His temperature rose late at night to a peak of 103.6° F. and fell in the early morning to nearly normal, with drenching sweats. Barlow became progressively weaker. Blood and mucus appeared regularly in the stools and urine. Urination became as frequent as every 15 minutes and the contractions of the bladder and the anus were accompanied by severe pain. During the 7th month after infection he was confined to bed at home and was able to sleep only under sedation. Nevertheless, Barlow made frequent examination of his own specimens and kept an almost daily record of his clinical and laboratory observations.

At the end of the 7th month the disease passed from the acute to the chronic stage. All the symptoms remained but in diminished force. In the tenth month, unable to conduct the field experiments for which he had contracted the disease, Barlow began treatment by intramuscular injections of Fouadin, a drug containing antimony—and considered a less risky treatment than the potassium antimony tartrate discovered to be a cure in 1918.

The Fouadin treatment lasted 8 days and was accompanied by a persistent asthmatic cough and nausea. Two weeks after completion of treatment, eggs ceased to be passed. The treatment proved only temporary. Four weeks later live eggs were again found in the urine. A second series of injections of Fouadin were taken over 19 days. Again the eggs disappeared, only to reappear three months later.

At this point Barlow decided to take potassium antimony tartrate (Tartar Emetic) as a cure. Though the French surgeons in the Egyptian campaign used Antimony as a cure-all, it is a highly toxic poison that must be given in small doses. The current practice is to inject it into the veins. At best P.A.T. makes the patient ill. At worst, according to Barlow, if it gets into the tissues during an injection, it can produce swelling and destruction serious enough to warrant amputation.

Barlow returned to Egypt for the P.A.T. treatment because, as he has written, he feared injury from American physicians who were not used to administering the drug. His experience even in Egypt is not likely to advance P.A.T. as a cure.

"If anybody ever tells you that the treatment is not too bad," Barlow has written, "advise them to take only one injection and report later. It is filthy and I have inside information. I used to sit with my watch in hand checking the injection. As soon as it was made it took from 5–7 seconds before I began to salivate and then but a few minutes before I began to cough or to vomit. All that day I was fearfully nauseated. On the following day the nausea began to subside only to come back in full force on the subsequent day of injection. No wonder the little boys and girls run away from it. No wonder that the men and women go only halfway through with the treatment."

Barlow took the complete treatment for 24 days, in all that time taking a total of only 1.5 grams of P.A.T.

Among the other effects he suffered as a result of the treatment were: muscular cramps, poor coordination, itching and swelling, pain in the face and teeth, urinary infection, coronary sclerosis, and impairment of hearing. The treatment was finished in December of 1945, a year-and-a-half after his initial infection. No eggs have reappeared. In 1947 Barlow was operated on for enlargement of the prostate, a
condition that assumedly resulted from the disease.

At present there is no drug as effective in treating Bilharziasis as P.A.T. Even if there were, however, it alone would not succeed in wiping out the disease. The areas in which Bilharziasis is endemic are primarily underdeveloped agricultural areas where the people, just as they did in El Marg in 1915, come in direct contact with the streams and canals in which the intermediate snail hosts breed. Were these people to be cured, many of them, in order to live, would return immediately to the waters and be reinfected.

Ironically, the technical advance of civilization in these areas has proved to be a detriment. The greatest expansions of the disease have been caused by the installation of dams and irrigation systems which in effect only enlarged the areas and number of people reached by infected waters. In Southern Rhodesia the Umshandige Irrigation System had to be abandoned in 1939 after it helped spread the disease to almost half the nation's population. A similar expansion of the disease occurred in the Gezira area of the Sudan, which was almost free of Bilharziasis until an irrigation system with 2,600 miles of canals was built in 1927. By 1945, 21% of the adults and 45% of the children had Bilharziasis. In Brazil, in the area around the new capital of Brasilia, the pattern is being repeated.

One authority on Bilharziasis, Professor Henry van der Schalie, Curator of Mollusks at The University of Michigan, has predicted that unless the disease is conquered or effective means of control are discovered, the increase in Bilharziasis caused by the new Asswan Dam in Egypt will cancel any economic benefits that the dam may yield. The Asswan Dam will form a lake almost 300 miles long, serving as a reservoir to feed innumerable irrigation canals. These new waterways will become part of the Nile system, contiguous with already infected waters. The result, an extension of the habitat of the snail intermediate host and the spread of the disease. Especially unfortunate will be the spread of the intestinal form of the disease (Schistosoma mansoni) to Upper Egypt where it is not common.

Attempts to eradicate the disease by destroying the snail and by interrupting the life cycle of the worm, were begun by Leiper in 1914. To date they have proven to be expensive and ineffective. Van der Schalie, who participated in a recent snail eradication program sponsored by the World Health Organization and the Egyptian government, has pointed out that although the project succeeded in temporarily lowering the number of infected canals and drains, two years later the "snail population was back to such a high level that one could not detect the tract had ever been treated." The primary reason for failure is that snail eradication must be 100% perfect to prove effective. One snail, in a matter of eight months, is capable of being the ancestor of 3½ million snails.

Another possible, though improbable, solution would be the overnight construction of sanitary plumbing facilities and pure water sources, accompanied by an immediate change in the economically and religiously determined life habits of the people who live in the midst of hitherto underdeveloped areas.

More realistic efforts, however, are aimed at interrupting the life cycle of the worm or discovering a vaccine that will make humans immune to the disease.

In one endemic area, Puerto Rico, biological control is being attempted by introducing an exotic snail that competes for natural food with the schistosome-bearing snails. A more speculative method of biological control may be achieved some day by introducing into the infected waters a snail that would attract the miracidia of the schistosome worm, but that would not enable them to evolve into the cercariae that invade men. To date, such snails have not been found.

The scope of research on Bilharziasis or Schistosomiasis multiplies almost as greatly as the worm itself. Between 1949 and 1958, 2,781 technical papers were written on the disease. They represent the continual search for molluscacides to kill the intermediate host—the snail, for drugs that will cure the disease more kindly than P.A.T., for means of biological control that will interrupt the life cycle, for methods to educate the inhabitants of endemic regions in sanitary and preventive measures, and for a vaccine that will provide immunity to Bilharziasis.

In the meantime, the race is to the snail and the worm he carries with him.
A CERCARIAL VACCINE
TO PRODUCE IMMUNITY
TO SCHISTOSOMIASIS

PHOENIX PROJECT No. 54

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Two experimental observations justify the attempt to find a means of artificially immunizing people against schistosomiasis. The first is the evidence of natural immunity in humans; the second is the evidence of immunity in animals. In areas where schistosomiasis is endemic, where the infection rate is almost 100 per cent, there are individuals who show a resistance to the disease. An experiment conducted in the Congo in the 1930’s is a case in point. Six volunteer fishermen who did not have schistosomiasis, yet who lived in an area where almost everyone did, were not infected when exposed to living cercariae. The cercariae penetrated their skin, a few grew into adult worms and laid eggs for a brief period. Then all symptoms of the disease disappeared. Similar evidence of animal immunity comes from mice and monkeys that, after having been once infected with schistosomiasis, were reinjected and subsequently demonstrated a significant degree of immunity to the second attack. Both the human and animal examples of immunity suggest that natural infection may stimulate a resistance against future exposures to schistosomiasis. An assumption follows that if immunity can be produced by natural infection it may possibly be produced by artificial means, by exposing people to something less than the disease itself.

The general immunizing mechanism depends on the body’s ability to resist a foreign substance. The entrance of such a substance has what is called an antigenic effect—it stimulates the manufacture of antibodies whose purpose it is to combine with specific antigens and neutralize them. If the antibodies succeed, the disease makes no progress. If the antibodies fail, the disease flourishes. Exposure—either natural or artificial—that produces an antigen-antibody reaction may build up enough antibodies to provide immunity to a specific disease.

Early investigators attempted to produce immunity to schistosomiasis in animals by using “vaccines” made from dead worms, extracts of dead worms and metabolic products given off by live worms. The injection of these substances into laboratory animals produced a limited immunity.

A less conventional method of artificial immunization, one that comes closer to the disease itself, is being investigated under Phoenix Project No. 54. The project’s key tool is radiation and the detrimental effect it has on living matter. Radiation is being used to impair the infective larval form (cercaria)
of the schistosome worm so that it cannot complete its life cycle. The radiation dose, however, is low enough so that the larvae, when injected as a "cercarial vaccine," can migrate through the tissues of the host. Thus the larval form with its secretions may possibly serve as a wide spectrum of antigens against which antibodies may be formed—one or many of which may provide immunity to schistosomiasis.

The possibility of using radiation to produce immunity in laboratory animals was demonstrated by the same group of investigators at the Phoenix Project in 1955 during a series of experiments on the round worm Trichinella, a parasite acquired when people eat improperly cooked infected pork. In these experiments it was demonstrated that when rats were fed larvae of Trichinella, irradiated with doses large enough to prevent reproduction, the rats acquired immunity to reinfection.

Similar experiments in England in 1959 on a disease of cattle caused by a lungworm successfully produced an effective "vaccine" made from the irradiated infective form of the worm.

The ground rules under which the schistosomiasis work is done were learned in the earlier work with trichinosis. In those experiments it was seen that too much radiation was as useless in producing immunity as none at all. Three conditions were observed.

1) Larvae that did not receive enough radiation would grow into sexually mature adult worms capable of reproduction. When fed to rats such larvae would give the animals trichinosis.

2) Larvae that received too much radiation would not fully develop. When fed to rats, these larvae, while not causing the disease, were ineffective as an immunizing agent.

3) The third condition was ideal—the irradiated larvae, when fed to rats, would grow into sterile, partially active adult worms and would produce an immune reaction.

Studies on a live irradiated "cercarial vaccine" against schistosomiasis center on producing a comparable third condition—finding the amount of radiation that would keep cercariae from developing into adults but which would not prevent a partial migration in the body. It is necessary to keep the cercariae from developing into mature adults so that eggs cannot be deposited in the tissues of the body and thereby produce the disease.

The first series of tests attempted to locate the radiation doses which would impede or prevent the growth of adult worms. In the initial experiment, mice, divided into five groups, were each inoculated with 300 cercariae of mixed sexes. The first group received non-radiated cercariae; the second group received cercariae exposed to 1000 rep (roentgen equivalent physical); the third group, cercariae exposed to 2500 rep; the fourth group, cercariae exposed to 5000 rep; the fifth group, cercariae exposed to 7500 rep. Eight weeks later the mice were killed and their livers and mesenteric veins examined for adult worms.

The mean (geometric) number of worms per mouse recovered was 51.5 from the non-radiated group; 29.0 from the 1000 rep group; 1.5 from the 2500 rep group and 0 from both the 5000 and 7500 rep groups.

These results indicated that a "cercarial vaccine" made of cercariae irradiated with 5000 rep would not give an animal schistosomiasis. One made from cercariae irradiated with 2500 rep would be almost as effective in preventing the growth of adult worms. A second experiment was conducted to see if immunity was produced by irradiated cercariae exposed to a range of doses.

In this second experiment, five groups of mice were similarly inoculated with non-radiated cercariae and cercariae exposed to 1000, 2500, 5000, and 7500 reps. After 8 weeks, each animal was given a challenging infection of 300 non-radiated cercariae of mixed sexes—more than enough to give them a heavy infection of schistosomiasis if they had not acquired immunity from the first inoculation. At the same time, a sixth group of uninoculated mice was infected with 300 non-radiated cercariae to test the infectivity of the cercariae used in the experiment. Four weeks after the challenging infection, the mice were killed and examined for adult worms.

The mean number of worms recovered per mouse after the challenging infection was 46.4 from the non-radiated group; 33.8 from the 1000 rep group; 6.6 from the 2500 rep group; 27.3 from the 5000 rep group; and 38.2 from the 7500 rep group. The mean number of worms recovered from the uninoculated mice that received only the challenge infection was 58.0.

This experiment showed that cercariae exposed to 7500 rep were ineffective; the cercariae were apparently too damaged to stimulate an immune reaction. Cercariae exposed to 5000 rep produced a
A microscopic section of liver from a mouse showing the foci of infection about a schistosome egg. The egg is the dark-stained object. The circular area surrounding the egg has been built up by the body as a reaction. Concentrations of such areas in a particular organ cause severe pathological changes. The thorn of this egg may be seen on the upper left side.

small measure of immunity, while cercariae exposed to 2500 rep produced a marked immunity. 1000 rep appeared to be too little radiation to be effective, the number of worms recovered from this group being almost as high as from the noninoculated group.

In a third experiment, the effect of two inoculations of radiated cercariae was compared with that of one inoculation. The cercariae had been exposed to 3000 rep.

The mice that received single or double inoculations of radiated cercariae but were not reinfected with schistosomiasis produced negligible average numbers of worms (0.8 and 0.4, respectively), all of which were sexually sterile, incapable of producing eggs. Two groups of similarly inoculated mice were then infected with 200 non-radiated cercariae. The average number of worms recovered from mice inoculated once and then infected was 8.0. The average number from those inoculated twice and then infected was 5.2. The average number of worms recovered from a control group inoculated only with non-radiated cercariae, was 59.6.

These results together with examinations of microscopic sections of the livers indicated that mice inoculated with cercariae which have been exposed to 3000 rep develop marked, but not total, immunity to schistosomiasis. The results of the whole series of tests are encouraging enough to warrant further investigation in four areas.

1) More precise determination of the most effective radiation dose. Such a study would cover doses of 2500, 3000, 3500 rep and even finer subdivisions.

2) Determination of the optimal number of irradiated cercariae required to produce immunity. All tests to date have been made with 200 or 300 cercariae. It is possible that a larger number of irradiated cercariae would be even more effective in producing immunity.

3) Determination of duration of immunity. It is necessary to learn the time pattern required for immunity to develop in the host, the time of maximum immunity and how rapidly, after peak effectiveness, the immunity may be lost.

4) Longevity of mice infected with large doses of irradiated cercariae. It would be desirable to test the effect of large numbers of irradiated cercariae on the longevity of mice when compared to mice inoculated with equal numbers of non-radiated cercariae and when compared to noninoculated controls.

Should these investigations yield favorable results, further studies need to be carried to other animals such as rabbits and monkeys, and eventually to man. If ultimately successful, artificial immunization may lessen the danger of schistosomiasis among the inhabitants of areas in which the disease is endemic.

(The cercariae employed in this investigation were Schistosoma mansoni, obtained from snails native to Puerto Rico. They were reared in a campus laboratory by Professor Henry van der Schalie, Curator of Mollusks at The University of Michigan Museum of Zoology.)
One way to interrupt the life cycle of the schistosome worm and eliminate schistosomiasis is to eradicate or control the large populations of snails that serve as the worm's intermediate host. Though this was realized as soon as snails were identified as carriers of schistosomiasis, fifty years of research have not produced an effective method of control. The seemingly docile snail has proven to be both a hardy and prolific beast.

The primary reason for this failure is attributed to the lack of information about snails in general and about the species that carry schistosomiasis in particular. This lack is being filled by a number of research programs throughout the world, one of the most prominent of which is conducted in the Mollusk Division of the University Museum of Zoology.

In the Museum laboratories, almost every species of snail known to host the disease is being raised and infected with schistosome worms. In addition, two species of American snails thought to be related to the snails that serve as host for the Asiatic variety of schistosomiasis, Schistosoma japonicum, are being studied—first, to assess the danger of an outbreak of schistosomiasis in America, and second, should these snails prove to be generically related to the Asiatic snails—that is physically and chemically similar—to develop methods of snail control and eradication that could be applied in endemic areas abroad.

The fear of schistosomiasis establishing itself in this country is not based on hypochondria. At the close of World War II a number of servicemen, as well as dogs used by the Armed Forces, returned from the Pacific Theatre infected with Schistosoma japonicum. If the schistosome larvae hatched from the eggs excreted by these men and these dogs could find a suitable snail host, the worms could develop through the second stage of their life cycle and reach the form that infects man. The fact that two American species of snails are suspected of being potential carriers increases the seriousness of the problem. The two suspects are the Pomatiopsis cincinnatiensis snail and the Pomatiopsis lapidaria snail; the former found in a range extending from southern Michigan to southern Kentucky; the latter in a wider range throughout most of the United States east of the Mississippi River. Early research on these two species revealed that their ecology, anatomy, and life habits had striking similarities to those of the Oriental Oncomelania snail that is the host for S. japonicum.

The potential threat carried by these snails is emphasized by the history of a lung fluke that is endemic in humans and animals in the Orient. This worm, which normally uses Oriental Oncomelania snails as its intermediate host, has successfully used the American P. lapidaria snail as a host and has been found in animals in the Ann Arbor, Michigan area.

Because the sanitary and agricultural practices in this country preclude the possibility of large numbers of people coming in contact with the streams and rivers that serve as the habitat of the likely snail hosts, there is no danger of a widespread schistosomiasis epidemic. There still remains, however, the possibility of a minimal amount of contact between humans and snail habitats through occasional activities such as swimming. More significant than the possibility of human infection is the likelihood of animal infection, for the Asiatic schistosome worms can use mammals, such as dogs, cattle, or rodents, as a final host. This establishes the possibility of an animal reservoir of infection building up to a point where it could become a localized health hazard to people.

In order to establish the validity of the suspected relationship between the American snails and the Oriental snails, a series of extensive field and laboratory experiments were begun in 1955 by Dr. Henry van der Schalie.

The experiments first accumulated as many facts as possible about the two American species by studying colonies of these snails found near Ann Arbor and Clinton, Michigan. Data taken in the field covered such details as the nature of the snails' habitats—the soil texture, temperature range, and moisture content—the snails' egg-laying habits, and their reproductive patterns. Eggs taken from these
colonies were hatched in the laboratory in order to conduct controlled experiments on such complicated snail characteristics as responses to temperature and moisture changes. In addition a series of experiments were conducted to see if the American species and the Asiatic species would cross breed. Success in these experiments would indicate a close relationship, for animals of different genera do not interbreed.

In the experiments, males and females from the two American species were placed in isolated laboratory environments where they could breed with each other and with males and females from the four Asiatic species that exist separately in China, Formosa, Japan, and the Philippines. Only the male P. lapidaria was successfully mated with females from the Philippine species and the Formosan species of the Oncomelania snails. The hybrids of P. lapidaria and the Philippine species even produced a second generation. The negative results in the other attempted cross breedings cannot be regarded as final for they may have been due to difficulties in maintaining the snails in the laboratory. The snails' complicated responses to such factors as temperature and humidity are not as easy to accommodate in a laboratory as they are in nature where the snail, given a wide range of choices, often can migrate to the conditions needed for survival.

It is interesting to note, however, that the two American species did not cross-breed in the laboratory. This failure may support field observations made at a site on the River Raisin where colonies of the two species overlapped, a rare occurrence because of their different natural habitats. Samples taken at the River Raisin over a period of three years revealed no evidence of cross-breeding. From this field experiment and the laboratory cross-breeding experiments, it appears that the American P. lapidaria snail may be more closely related to the Oriental snails than it is to the American P. cincinnatiensis snail.

At present a series of experiments is being conducted to test the receptiveness of the two American snails and the hybrids to the larval form, the miracidium, of the S. japonicum worm. These infestation experiments are similar to a series that took place in the 1940's at the National Institutes of Health, which succeeded in infecting the American P. lapidaria snail with the Chinese strain of S. japonicum. Professor van der Schalie's group at the University, in a later experiment, was able to infect the P. cincinnatiensis snail with the Japanese strain of S. japonicum, the miracidia entering the snail and developing into the next stage, the sporocyst, but not further. These results are not conclusive proof that infection would occur in nature were the eggs of S. japonicum to hatch in a snail habitat, but they are a strong indication that it is possible.

As a result of this series of experiments, a paper has been written by Lowell Getz on a theoretical method by which S. japonicum may find a focal point in this country. His conclusions were based on matching the life habits of the two species of snails with the life habits of mammals that might serve as final hosts to S. japonicum. The P. cincinnatiensis snail, because it lives on river banks, and is in water only during heavy rains or floods, appears to be an unlikely host. Its chances of being infected and in turn serving to infect animals are too limited. River banks are infrequently visited except by muskrats, which do not exist in large numbers. Also, the high water conditions when the snail is in the river would most likely wash away the miracidia that would infect the snails as well as the cercaria that would infect humans.

P. lapidaria, the species successfully cross-bred with the Oriental snail host, lives in a more amenable environment—marshy seepage areas where puddles of standing water are always present and where large populations of meadow voles abound. Since these voles do not avoid going through water, the right conditions exist for completing the life cycle of S. japonicum. Infected snails could shed cercariae in the pools and puddles. The voles, moving through the water, could become infected and serve as the final host during the adult and egg-laying stages. Similarly the infected vole, in moving through the seepage areas, could pass the eggs into an environment ideal for their finding the snail intermediate host and completing the life cycle.

The fundamental purpose of this research on snails in general and the schistosome-bearing snails in particular—is to illuminate the nature of mollusks, not to emphasize the possibility of the disease occurring in America. The basic information gathered by the Museum group, when applied to problems of schistosomiasis throughout the world, as well as to other parasitic diseases for which snails serve as intermediate hosts, may be useful in finding ways of controlling snail populations and alleviating human misery.
The drawing is the *P. cincinnatiensis* snail that may be able to host schistosomiasis in America. Snails of the same genus are shown in a laboratory vivaria at The Museum of Zoology.
COVER: A reproduction of a Phoenix from an ancient Egyptian cake mold.

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