ROCKY MOUNTAIN LABORATORY

A Brief History of its Growth and Research Activities

National Institute of Allergy and Infectious Diseases

Dr. H. T. Ricketts in 1906 successfully induced Rocky Mountain spotted fever in an experimental animal—the guinea pig—and then showed that ticks, allowed to feed on a sick animal, could transmit the disease to a well one. Dr. Ricketts, who died of typhus at an early age, was honored for his pioneering work by having named after him the group of organisms—rickettsiae — causing spotted fever and other rickettsial diseases throughout the world.

early history

Tucked into the foothills of the rugged Bitterroot Range of the Rocky Mountains is a unique research facility of the U. S. Government. At this laboratory of NIH's National Institute of Allergy and Infectious Diseases, more than 35 scientists and their assistants study a number of important diseases, including those in nature communicable to man by ticks, insects, or lower animals.

The story of today's Rocky Mountain Laboratory has its beginning in the 19th century when fear of a mysterious and generally fatal illness threatened the prosperity of a rapidly growing section of western Montana, the Bitterroot Valley.

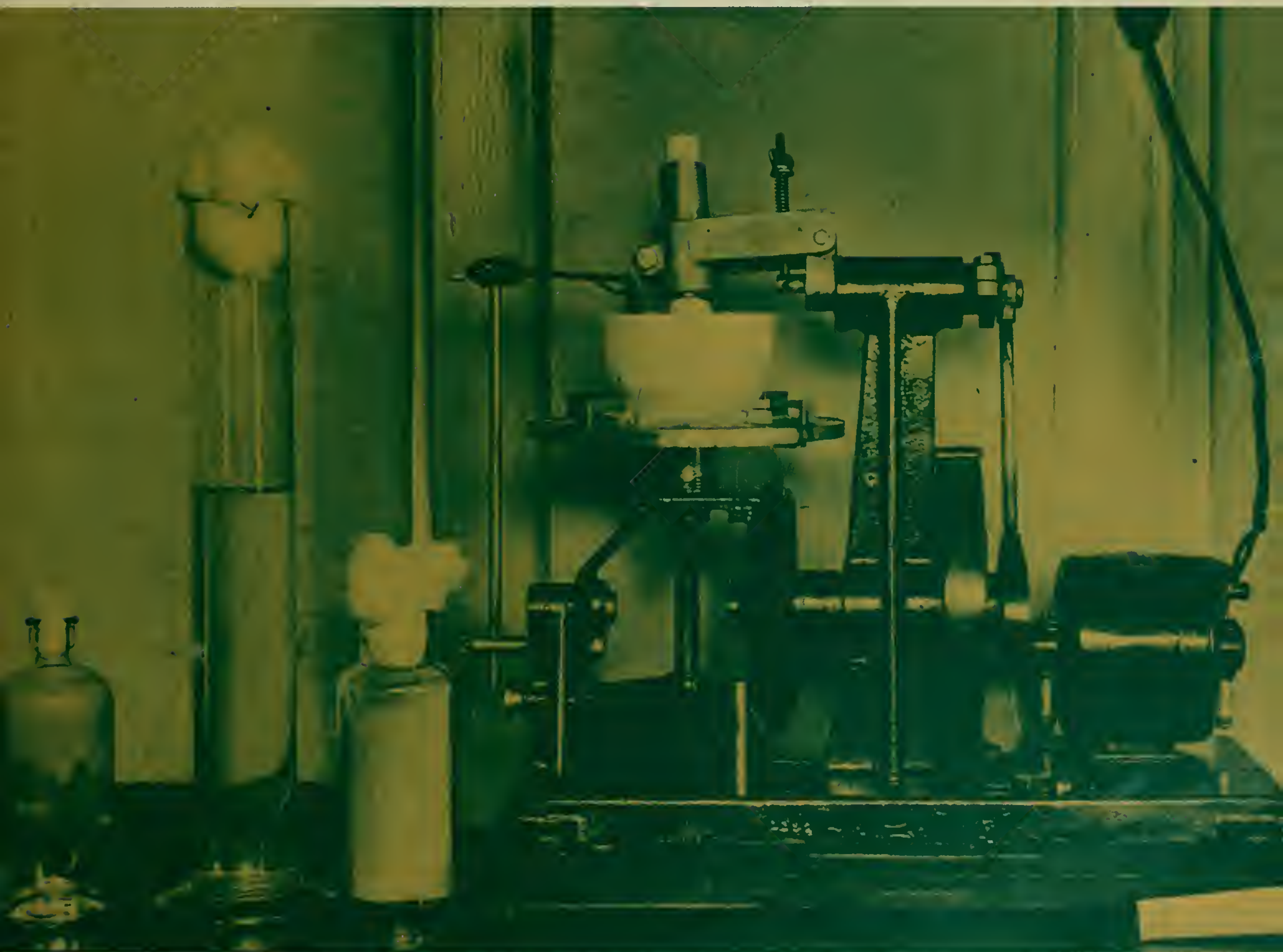
This beautiful country had first been explored by Lewis and Clark in 1805 and again in 1806. By 1890, the explorers had been followed, first by missionaries, and then by ranchers and farmers. Fertile fields were under cultivation and shipments of fruit from productive orchards were started to markets back East. Cattle grew fat on free pasture back in the canyons and on the lower slopes of the mountains. A land boom was underway as more and more settlers were attracted to the valley from Missouri and other states.

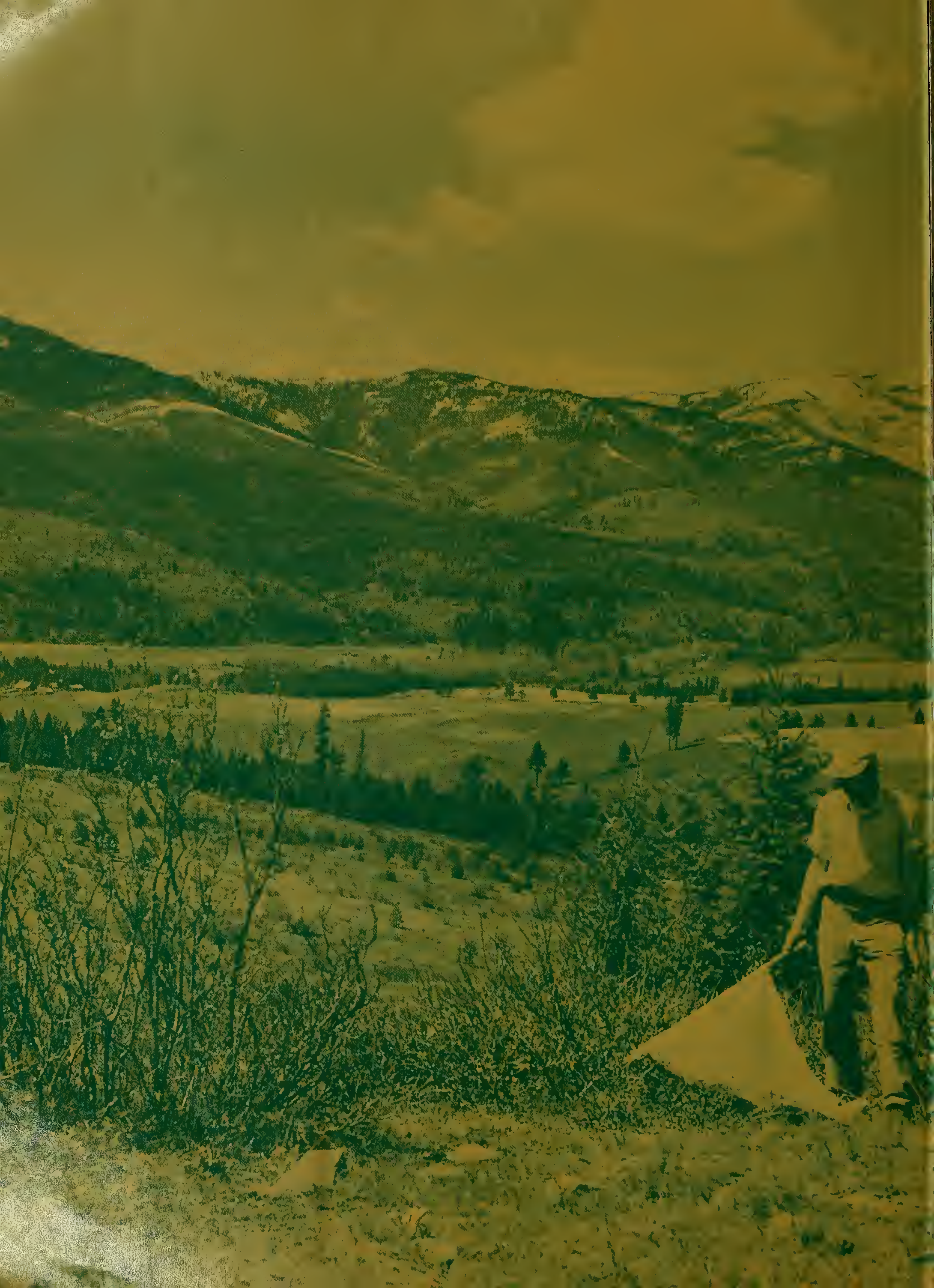
With the early settling of the Valley, a disease called "spotted fever" or "black measles" began to appear each spring and early summer. Most people blamed it on drinking water from melting snow from the mountains. A few thought the causative agent would be found in the sawdust piles of the lumber mills. But, whatever its origin, about 80% of all spotted fever cases in adults were fatal, and in 1901 the people of the Bitterroot appealed to their governor for help in controlling this disease. At his direction, the newly created State Board of Health began a campaign which was to enlist the efforts of health scientists for years and create one of the most exciting chapters in medical history.

In 1910 this shack on a deserted farm in the Bitterroot Valley served as a laboratory for scientists called to Montana to help solve the problem of Rocky Mountain spotted fever.

In 1921, the U. S. Public Health Service equipped as a laboratory an abandoned schoolhouse near Hamilton, Montana. In this building, during the years it was in use, several workers fell victim to spotted fever in the course of research leading to the development of an effective vaccine against the disease. Today the schoolhouse is owned by a retired RML scientist and has been converted into a museum documenting research contributions of RML.

Before antibiotics were found effective against spotted fever, the Rocky Mountain Laboratory manufactured large quantities of vaccine which were shipped out, on request, to physicians all over the country. This tick-grinding machine was used in early vaccine development work.





A flannel flag drawn slowly through tick-infested underbrush in the valley and on the lower slopes of the mountains picks up hundreds of ticks for RML studies. Traps baited with "dry ice" are also used since ticks are attracted by carbon dioxide whether given off by the human body or released by evaporation of the "dry ice" chemical.

SPOTTED FEVER RESEARCH

The U. S. Public Health Service was brought into the story early when, at the request of the Montana State Board of Health, Dr. John F. Anderson, a PHS officer from Washington, D.C., joined Drs. L. B. Wilson and W. M. Chowning, pioneer investigators who had come out to Montana from the University of Minnesota. Dr. Anderson corroborated findings of these earlier scientists that the wood tick (known scientifically today as *Dermacentor andersoni*) was an important factor in transmission of spotted fever to man.

In the years that followed, research on the disease was continued by such outstanding scientists as Dr. Howard Taylor Ricketts of the University of Chicago and Dr. R. A. Cooley of Montana State College. The role of the Public Health Service varied. During World War I, for example, other problems of overwhelming importance diverted PHS attention from spotted fever and the State of Montana was left to carry on the battle alone. By 1921, however, the disease had been identified in states other than Montana and the Public Health Service was urged to return to support of research on the problem.

Dr. Ralph R. Parker, of the Montana State Board of Entomology—an agency created in 1913 to study and control diseases disseminated by "insects"—had spent seven years studying ways to eradicate the wood tick. He was hired by the Public Health Service to set up an official field station in an abandoned school building in the Bitterroot Valley, near Hamilton, Montana. Dr. R. R. Spencer, a research physician, was then sent by the Public Health Service to Hamilton to take charge of the schoolhouse laboratory and work with Dr. Parker on the development of a spotted fever vaccine.

In 1928, the State of Montana completed in Hamilton a modern research laboratory to house the control work of the State Board of Entomology and the expanded work of the Public Health Service. The new building was first leased and then purchased by the Public Health Service.

At the Rocky Mountain Laboratory a successful vaccine was developed and produced there until manufacture was taken over by commercial laboratories. Later, when it was found that antibiotics could cure spotted fever, use of the vaccine became limited to those persons excessively exposed to the wood tick. RML scientists continue to study the disease in an effort to find answers to fundamental biological questions—answers which will help bring under more effective control, perhaps, many of the infectious diseases which continue to plague man.

the present laboratory

In 1948 the Rocky Mountain Laboratory became a part of what is now known as the National Institute of Allergy and Infectious Diseases, one of the components of the National Institutes of Health. Unique among NIH laboratories, most of which are located in Bethesda, Maryland, the Rocky Mountain Laboratory is the largest in NIAID's intramural program.

Situated on a 33-acre tract of land on the edge of Hamilton, Montana, the main laboratory building has been enlarged twice. Its location in the open country of western Montana makes possible rather extensive animal quarters and also facilities which enable scientists to work with highly transmissible agents. For more than 40 years the laboratory has, thus, provided a stimulating environment for Federal investigators interested in the interrelationships of disease agents, wild and domestic animals, and man.

Headed by a director, the staff of Rocky Mountain Laboratory is divided into ten sections. Current major research interests include: diseases having a reservoir of infection in the natural environment; medical entomology (the study of arthropods as transmitters of disease); certain chronic viral diseases; immunology of tuberculosis and other infectious diseases; the structure, composition, and role of microbial constituents in the disease process; and the immune and other host responses.

A detailed drawing of a mite is prepared by an artist working with a specimen visible only through a microscope. Such drawings are valuable to RML experts who have identified and named many of the New World varieties of the more than 2,000 known species of mites.

Rocky Mountain Laboratory research often depends upon field investigations. In this series of photographs a scientist is shown gathering evidence that the organism causing tularemia may grow in the mud and leaf mold of streams. (1) A water sample is collected from a creek that flows into a suspect stream. (2) More samples are taken from a location below creek entrance. (3) The temperature of each sample is carefully noted on each bottle. (4) Water samples are injected directly into mice which are then closely observed for signs of disease.

Collaborative studies with foreign scientists are routine for RML investigators since the laboratory has been designated by the World Health Organization as a Regional Reference Center for Human Rickettsioses. This camel is being used in experiments conducted by American and Egyptian scientists to investigate the role of livestock in the spread of typhus in areas where the disease commonly occurs.

DISEASES IN NATURE

Many diseases in nature, like spotted fever, are caused by microorganisms midway between bacteria and viruses. These infectious agents are called rickettsias in honor of the pioneer spotted fever scientist, Dr. Howard Taylor Ricketts. The rickettsial diseases have been divided into four main groups on the basis of clinical, epidemiological, and immunologic features: typhus; spotted fever; scrub typhus; and Q fever.

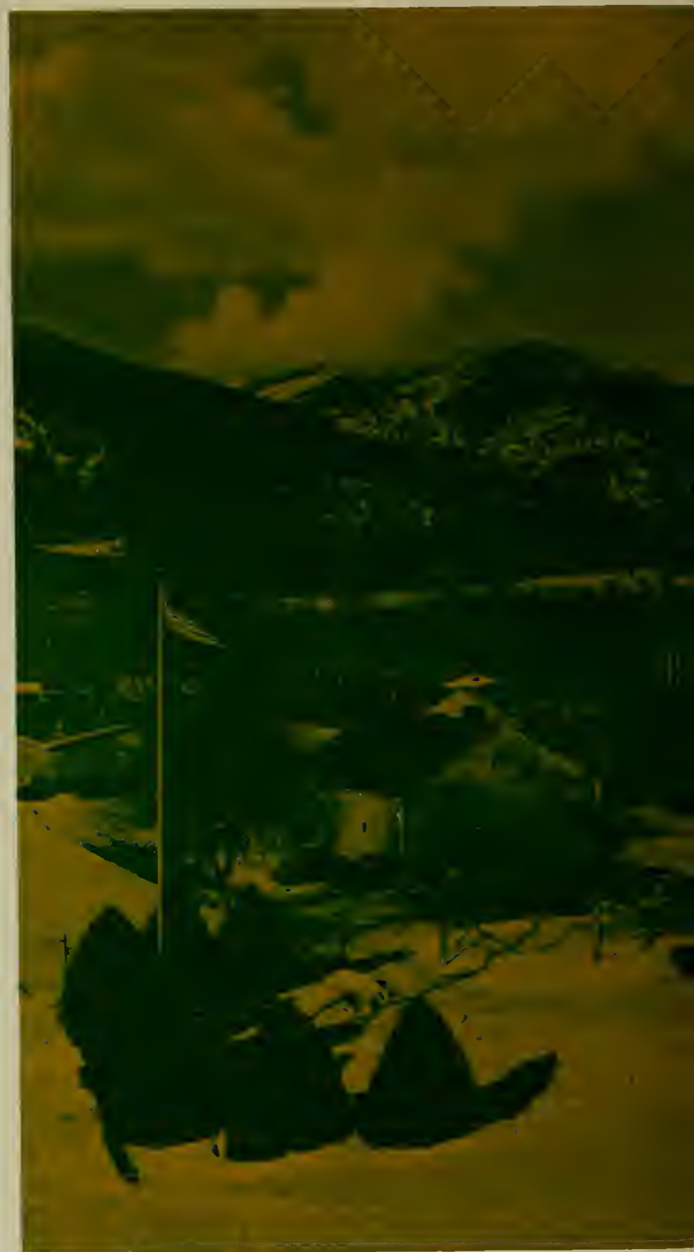
The Rocky Mountain Laboratory, because of its continuing interest in spotted fever and related diseases, has been designated by the World Health Organization as a Regional Reference Center for Human Rickettsioses. Laboratory staff members serve in consultant and collaborative capacities to scientists working on rickettsial diseases throughout the world.

For example, in collaboration with Canadian workers, RML scientists characterized a new species of rickettsia isolated from rabbit ticks as belonging to the typhus group. This agent may be related to that causing typhus in Egypt where the possible role of livestock in spread of the disease is being studied. Parallel studies of the epidemiology of typhus in South America have been conducted by RML scientists in collaboration with representatives of the Pan American Health Organization.

By studying the immunogenicity of the two phases of the organism causing Q fever, scientists representing RML and AFEB (Armed Forces Epidemiology Board) have developed a promising experimental vaccine which induces a high level of resistance to the Q fever rickettsia. The Australian government is interested in using this vaccine in highrisk occupational groups in that country.

Other animal diseases transmissible to man include tularemia and rabies. RML scientists have some evidence that the agent causing tularemia (rabbit fever) may grow in the mud and leaf mold of streams, but the complex life history of this organism is not fully understood.

RML investigations of rabies in Montana bats represent one of the longest continuous series of studies of the disease. Scientists at RML have been particularly interested in the immunologic aspects of rabies and the spontaneous recovery of some animals from this disease. This latter problem is being investigated by a staff member working temporarily in Argentina where rabies is common. He is collaborating with the staff of the Pan American Zoonoses Center in this project.



Today's Rocky Mountain Laboratory of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, is the largest in NIAID's intramural program.

Bats as carriers of rabies virus are of special interest to RML scientists. Members of one field team are examining bats captured in western Montana. Studies on rabies have taken RML investigators to South America and other parts of the world.

Two jars containing tick specimens are part of one of the world's largest tick collections. This museum at Rocky Mountain Laboratory is often visited by foreign medical entomologists who wish to become familiar with ticks native to their areas.

MEDICAL ENTOMOLOGY

Since many rickettsial and viral diseases are known to be transmitted to man by ticks, mites, and insects, it is important to have a thorough knowledge of arthropod vectors. For this reason, a number of RML scientists continue the laboratory's historic research on ticks, and are pursuing, with techniques not available to pioneer entomologists, answers to such questions as why do rickettsias grow so well in tick cells but not in cells of other arthropods. Answers to these questions may help explain why some viruses grow in man and others do not. In this respect, the tick may serve as an inexpensive test tube for answers to basic inquiries into the biology of viruses.

Stored away in drawers of cabinets lining the walls of a medium-sized room at Rocky Mountain Laboratory are vials containing one of the world's largest tick collections. This collection, begun in 1915 and added to by scientists all over the world, is invaluable in making accurate identification of ticks which may be vectors of diseases in man. Today, entomologists from the far corners of the earth visit or write the laboratory in order to become familiar with ticks native to their areas.

In addition to curating a collection representative of three-quarters of all presently known tick species, RML scientists raise ticks for their own research and that of others. This is not quite as large a job today as it once was when over a million adult ticks were needed annually to meet the demand for vaccine.

A chigger, or mite, collection rivals the one for ticks and is as invaluable in making comparisons for identification purposes. Over 2,000 species of chiggers, in one phase of their development, feed on animals. Although only 15 species are known to bite man, 4 of these transmit scrub typhus. To date, there is no evidence that chiggers in this country play a role in transmitting any disease to man.

Like ticks, chiggers are sent to Rocky Mountain Laboratory from all over the world for identification. RML experts, in fact, have named most of the New World varieties, and serve as consultants to the U. S. Department of Agriculture and the U. S. National Museum (Smithsonian) as well as to agencies and individual scientists in other countries.

CHRONIC VIRAL DISEASES

Several years ago, research at Rocky Mountain Laboratory took a new turn with the initiation of studies of chronic diseases of possible viral origin. These investigations are confined to the several animal models available: scrapie and progressive pneumonia in sheep, encephalopathy and Aleutian disease of mink. In these so-called "slow virus" diseases there is a long incubation period. It is hard to determine when an animal was first infected, but its condition worsens gradually over the months and years. The usual pathologic changes accompanying viral infections are absent at death and proliferative and degenerative lesions predominate in the tissues. A major objective of the studies is to gain an insight into the development of these diseases as the key to study of similar illnesses in man.

Because of the close biologic relationship between man and lower animals, it should not be surprising if man shared with animals a susceptibility to related slow viral diseases. Host responses in the four naturally occurring animal diseases mentioned above, and properties of the causative agents are the concern of RML scientists. At present, they are working with thousands of mice, several hundred sheep and goats, and about 700 mink, but they are trying to find appropriate tissue culture systems which will reduce this large number of animals that must be observed over long periods of time. Studies on the development of chronic diseases will, thus, be made easier and more precise and may provide valuable tools for gaining insight into the defensive mechanisms animals—including man—use against viruses.

MOLECULAR BIOLOGY

At Rocky Mountain Laboratory, complex tools have been devised for separating microorganisms, such as bacteria, into their component parts so important studies correlating structure with function can be carried out. A special hydraulic press for rupturing the cell walls of bacteria was designed by RML scientists. Known as the Ribi press, it is now in use in some 300 laboratories around the world. A new centrifugal chromotography technique which makes use of a tightly packed microparticulate gel for more effective

"Slow virus" diseases of sheep and mink are studied in animals such as these. Progressive pneumonia and scrapie in sheep and Aleutian disease and encephalopathy of mink are being investigated as models of counterpart diseases of man. The mink are housed in these recently constructed buildings.

Intact cell walls of bovine tuberculosis bacillus (shown here magnified 65,000 times) can be obtained from whole cells in the Ribi press. These cell walls are used in vaccine development studies.

At Rocky Mountain Laboratory, complex tools have been devised for separating microorganisms into their component parts. A RML scientist is shown in front of a special hydraulic press which he and his colleagues designed. Known as the Ribi press, it is now in use in some 300 laboratories.

separation of large molecules has also been developed by RML scientists. Their imaginative application of biophysical techniques to the study of microbial components is making a contribution to basic sciences far beyond the research problems of immediate concern.

Use of the Ribi press has greatly facilitated studies of endotoxins, bacterial products intimately bound to the bacterial cell wall. Guest workers come to Rocky Mountain Laboratory each summer to learn techniques for determining the chemical and physical characteristics of endotoxins of various organisms—many of which seem to have properties in common. These investigations are shedding light on basic immunological phenomenon.

ALLERGY AND IMMUNOLOGY

Basic inquiry is being made into the mechanisms of antibody formation, classes of antibodies, and the processes involved in the development and manifestation of delayed hypersensitivity phenomena.

However, among the more defined and practical objectives is the development of more efficient vaccines for tuberculosis and other diseases. Attempts to develop a more effective and safer TB vaccine have focused on studies of the cell walls of bovine tuberculosis bacillus (BCG), which is now used in live vaccines in some countries. RML scientists have found that a cell wall preparation by itself will protect animals against tuberculosis if the cell walls are in contact with oil droplets. Studies are being undertaken to find out why this contact with oil is necessary and to reveal other characteristics of the immunizing agent.

In studying the causative agent of whooping cough, *Bordetella pertussis*, other RML scientists have observed that injections of this bacillus produces in mice an immunologic state similar to that of allergic individuals. So far, investigators have not been able to separate this "sensitizing" factor from active antigen in *B. pertussis*. Elimination of the sensitizing factor may provide a safer vaccine against whooping cough in those countries where use of the present preparation occasionally produces encephalitis.

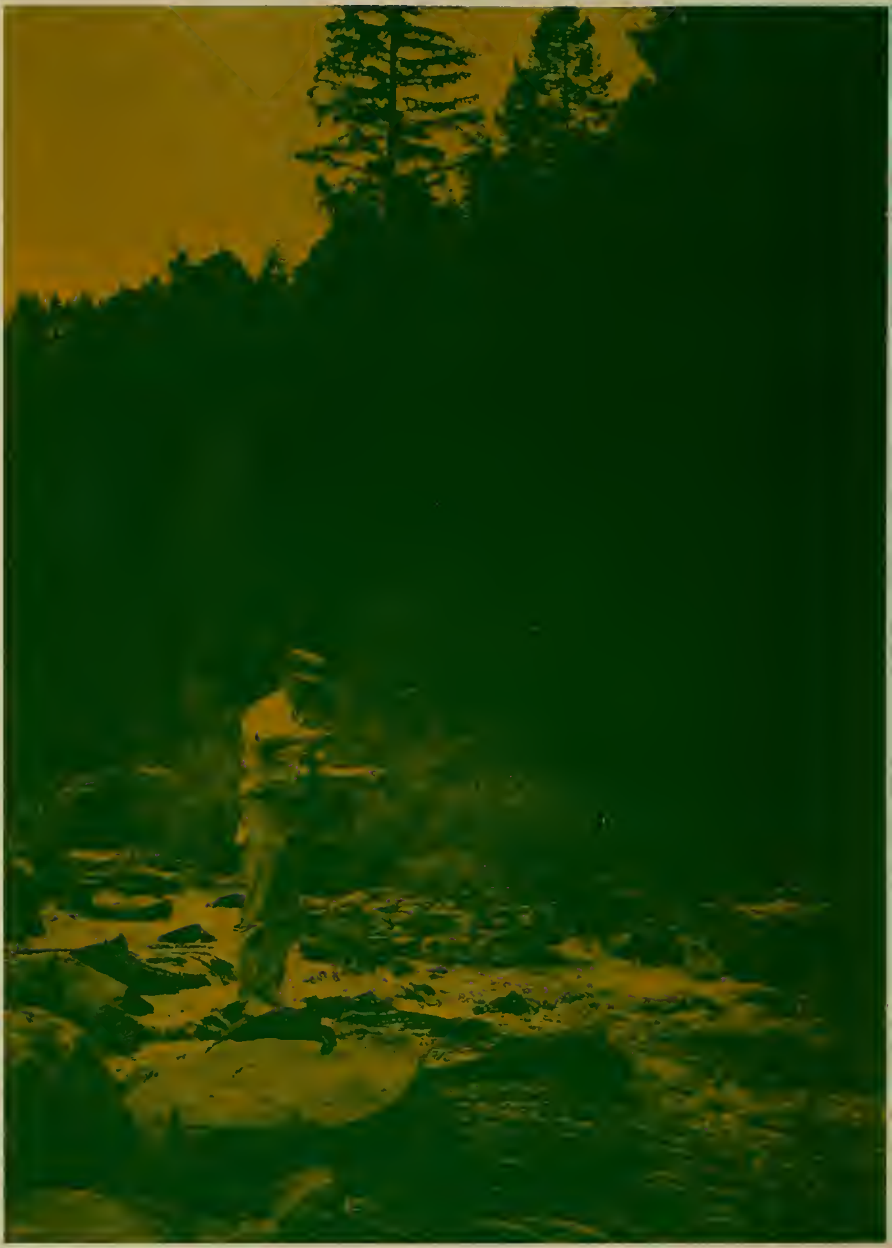
Many scientists at Rocky Mountain Laboratory collaborate in studies of the immunologic and environmental aspects of viral, bacterial, and rickettsial diseases. Some investigators are making attempts to develop arthropod tissue cultures for the study of these agents and to determine the role of cold-blooded vertebrates (snakes and frogs) in the natural history of encephalitis viruses. Other scientists focus on a group of agents known as chlamydiae. These organisms cause such diseases as psittacosis (parrot fever), trachoma (eye infection), and a form of venereal disease. A test for antibody to the antigen presumably shared by many chlamydiae was developed several years ago at Rocky Mountain Laboratory and has been used to study trachoma, a major cause of blindness in American Indians and other groups.

In addition to carrying out infectious disease research, scientists at the Rocky Mountain Laboratory sometimes conduct diagnostic tests for physicians and veterinarians in nearby communities when these procedures are within the scope of RML programs. Such public service is in keeping with the historic mission of this research facility and with the contributions its scientists have made to the health of our nation.

Some of these contributions are highlighted today in the old schoolhouse laboratory near Hamilton which has been converted—largely through the independent efforts of a retired RML scientist, Dr. William L. Jellison—into a museum. Steps leading to the discovery of the causes of illnesses such as spotted fever are documented in pictures and artifacts, and visitors are often surprised to learn that RML pioneers even lost their lives to the diseases they sought to conquer.

In the years to come, this museum may chronicle other achievements which, now, are represented only by searching inquiries and the answers sought by scientists engaged in current research projects at the Rocky Mountain Laboratory.

RML scientists have developed a radioisotope precipitation (RIP) test for detecting antibodies to polio viruses, Q fever rickettsia, and a group of agents known as chlamydia. In this photo, the RIP test is applied to serums taken during an epidemiological study of trachoma among American Indians, a disease caused by one of the chlamydia.



RML personnel enjoy unparallelled recreational opportunities in the rugged countryside with fishing, perhaps, the favorite sport.

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all, on the ground of race, color, or national origin, be
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am or activity receiving Federal financial assistance."
rogram of the Public Health Service, like every program
assistance from the Department of Health, Education,
in compliance with this law.

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