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Progress Report of Hemotropic Disease Research

May, 1971

From: Texas A&M University

and

Bogota, Colombia

Institute of Tropical Veterinary Medicine

College of Veterinary Medicine

Texas A&M University

College Station, Texas

A Synopsis

of the May 1971 Technical Progress Reports

on Hemotropic Diseases

Presented to:

Agency for International Development

and

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From:

Texas A&M University

College of Veterinary Medicine

Institute of Tropical Veterinary Medicine

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Concerning work done at:

College of Veterinary Medicine, Texas A&M University

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Laboratorio Investigaciones Medicas Veterinarias

Bogota, Colombia

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A Synopsis of the May 1971 Progress Report

on Hemotropic Diseases Research

The ultimate aim or goal of animal disease research is eradication of the disease or its agent, but until our knowledge reaches a point where this is practical or possible, compromise solutions to reduce losses with a degree of control are frequently necessary.

Of the hemotropic diseases, the anaplasmosis--babesiosis complex, presents the greatest single challenge in Latin America. The causitive agents of these 2 diseases have common vectors, and both are intraerythrocytic parasites which produce severe hemolytic anemias.

Research at Texas A&M has concentrated on the disease produced by A. marginale, whereas work in Bogota has been aimed primarily at babesiosis. It is essential that these agents be worked on separately in order to find the point where control and eradication is most feasible, however, it is increasingly clear that under field condition the disease syndrome often observed is a mixed infection of both Babesia and Anaplasma.

Studies of these disease agents have been approached to accomplish the urgent need for partial control first, with complete control and eradication to follow. The need for methods of protecting cattle from the ravages of these diseases has been given the highest priority, with the result that techniques have been developed which work well under controlled conditions. The following outline forms the basis for past, current, and future research, as applied to the goal of disease control.

Phase I: Partial control and elimination of death losses, due to hemotropic disease (babesiosis and anaplasmosis).

A. Survey work to determine the extent of the problem, the location of endemic zones, and the influence of geographic location and climatic conditions.

B. Premunition - with and without the use of drug therapy to moderate the premunizing infection.

C. Therapeutic trials aimed at moderating premunizing infection.

D. Determination of immunologic types of A. marginale and Babesia, especially as this pertains to successful premunition.

Phase II: Control of hemotropic disease - including the elimination of production losses, but short of complete eradication.

A. Vaccination.

1. An adjuvant killed vaccine that is effective and safe in the prevention of clinical anaplasmosis.

2. A live attenuated vaccine that is - capable of preventing clinical anaplasmosis, but incapable of natural transmission, or reversion to virulence.

B. Methods of vector control that would reduce the level of exposure below those needed for epidemic outbreaks, and the maintenance of endemic conditions.

Phase III: Eradication of anaplasmosis and babesiosis

A. Treatment aimed at completely removing the infection in carrier animals.

B. Vector control at a level adequate to prevent re-infection of clean cattle.

C. A more effective diagnostic test for the identification of carrier or infected animals.

During the past 3½ years of RF and AID support many research objectives within this outline have been successfully accomplished. The Texas A&M team has not worked on all phases outlined above, but has essentially completed Phase I, with the possible exception of sub-heading "D", and is currently involved with a field trial utilizing research information in this area. Objectives of Phase II and III are being studied, and while incomplete are resulting in information which will provide the essential links necessary to eventually formulate a program for complete control and eradication.

Implementation and utilization of research findings resulting from this program will be the final goal. The actual extension aspects or widespread field use of these findings while outside the scope of our current potential will hopefully be carried out by local agencies and veterinarians as research findings are better understood. The technology has now been developed which will allow individual livestock producers to greatly reduce their losses from these diseases. A concerted government program will be required before eradication can be accomplished, and from a practical point of view such an approach will be in the future.

We fully recognize that other major livestock, hemotropic disease problems exist in tropical latitudes. Two such diseases are trypanosomiasis, and theileriasis. Both of these problems are severe in Africa and parts of Asia. The absence of tsetse fly in South America has led to a false sense of security with regard to trypanosomiasis. In recent years <u>Trypanosoma</u>

vivax has been identified in Colombia, and is now being found throughout the country. This agent is being recognized as a disease entity to be concerned about. Many basic considerations, such as prevalence, vectors involved, and the extent of losses due to this agent are now under consideration by our group. To our knowledge theileriasis of cattle does not occur in South America.

Research studies are underway in Colombia on the pathogenic trypanosome, *T. vivax*. In Texas some work is being done on a non-pathogenic trypanosome, *T. theileri*, using this organism as a model to gain information that may be useful in future studies on *T. vivax*. For the same reason limited activities are underway studying a *Theileria* in deer, using this as a model for possible future studies on pathogenic theilerias.

Annual Progress Report of Hemotropic Disease Research

March 1970 to May 1971

Texas A&M University

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ANAPLASMOSIS

Past reports have covered in some detail the results of premunition and vaccination experiments as listed in Phase I and II. These studies have shown that the vaccines used and developed in the U.S. were inadequate in preventing anaplasmosis as seen in the endemic zone of the North Coast of Colombia. Premunition with virulent A. marginale did however produce a high degree of resistance. As a part of Phase I surveys revealed a high degree of correlation between the incidence of anaplasmosis and climatic conditions. The low altitude tropical areas had a greater incidence of anaplasmosis than areas near Bogota where the altitude was over 8,000 feet.

In addition to marginal potency, the use of killed vaccines for anaplasmosis, have in recent years been found associated with an isoerythrolysis syndrome in calves born to dams previously vaccinated. Reports indicate that this problem is caused by erythrocytic antigens present in the vaccine. To overcome this, efforts at concentrating or purifying these antigens have been and are now underway. A 4 fold concentration of antigens has been achieved, based on serologic activity. Actual vaccine trials have not yet been carried out. Evidence has also been uncovered that extra-erythrocytic antigens occur at some stages of infection. If sufficient antigens can be harvested from this source a vaccine free of erythrocytic antigens would be possible. A serologic method has been developed which may be useful to quantitatively test for the presence of extra-erythrocytic antigens.

Attempts to moderate the Anaplasma response in young calves by treatment, 14 to 21 days after exposure, with oxytetracycline (terramycin)

were unsuccessful. A combination of oxytetracycline and 356 C 61 (Burroughs-Wellcome Laboratories) was effective in moderating premunizing infections.

Comparisions have been made of A. centrale, A. marginale (virulent) and A. marginale (attenuated) infections induced in calves and adult cattle. The 2 vaccine strains (A. centrale and A. marginale (attenuated)) produced infections of about the same degree of intensity, in instances where infection could be measured by the usual parameters. The A. marginale (attenuated) had the disadvantage of failing to infect 30% of the young calves that were injected with vaccine material. This creates a difficult situation to predict since in field vaccination it may be impossible to check for evidence of premunition by the usual means, and if a high percentage of calves failed to react they would remain fully susceptible to future exposure to the virulent organism. Both A. centrale and A. marginale (attenuated) produced infections which were significantly milder than infections occurring from the virulent organism.

Therapeutic trials aimed at the complete elimination of infection in the carrier animal have been undertaken. Oxytetracycline fed daily for 45-60 days, or injected in large amounts for 12 consecutive days are known to eliminate the infection, but a faster more efficient treatment is highly desirable. A combination of oxytetracycline and an experimental drug 356 C 61 has been shown to be more effective than either drug alone. Anaplasma infections have been consistently eliminated in splenectomized calves treated 3 times at 24 and 48-hour intervals with 5 mg/kg 356 C 61, and 11 mg/kg oxytetracycline, given IV. A third new experimental drug designated 4A65 has shown promise in the treatment of anaplasmosis. A wide variety of drugs, combinations of drugs, with varying treatment intervals as well as dosage levels have been unsuccessfully

tried before arriving at what appears an optimum treatment. In some few instances a single treatment has been successful, but unfortunately this has not been consistent. Only limited trials have been conducted with intact animals, but evidence is present that the dose level for splenectomized calves is not always adequate for intact animals, and so some adjustments will be needed.

The elimination of carrier infection by the treatment described, raises the question as to the degree of susceptibility of treated cattle to re-infection. A group of splenectomized calves that had been infected, then treated so as to remove all evidence of infection, were re-exposed an average of 167 days after treatment and found to be fully susceptible, with no evidence of residual immunity. This is unfortunate since treatment then can only be successful if precautions are taken to eliminate future exposure.

BABESIOSIS

As a secondary effort, work on babesiosis has been conducted at Texas A&M, using Babesia rodhaini in mice, and Babesia bigemina and B. argentina at Nuevo Laredo.

Efforts to infect white-tailed deer with cattle Babesia either by blood inoculation, or tick infestation (Boophilus annulatus) using known infected ticks have been unsuccessful. Boophilus annulatus ticks coming from white-tailed deer have not been shown to carry Babesia infection.

Therapeutic trials against B. rodhaini have shown oxytetracycline and 356 C 61 to be ineffective, Ganaseg was effective and 4A65 highly effective. Toxicity studies showed 4A65 to have a LD 50 of 49.3 mg/kg, whereas for Ganaseg it was 89.2 mg/kg. The experimental drug 4A65 removed the infection entirely in most instances, whereas Ganaseg resulted in carrier animals. A sterile, partial immunity persisted 56 days in a 4A65 treated group. The carrier infection in a Ganaseg treated group, for the most part, persisted till the 112th day during which time immunity to challenge was complete. A residual, sterile immunity persisted in the Ganaseg group for about 28 days after the end of the carrier state.

Vaccine trials with B. rodhaini showed a highly antigenic preparation capable of inducing a significant degree of protection to virulent challenge.

TRYPANOSOMA AND THEILERIA

Work has also been done with Trypanosoma theileri and Theileria cervi, using these agents as models, hoping by such studies to gain further insight into the nature and problems of the pathogenic trypanosomes and theilerias. This work is reported in detail in the annual report dated May, 1971.

COLOMBIAN ANNUAL REPORT OF HEMOTROPIC DISEASE RESEARCH AND TRAINING

March, 1970 to May, 1971

Instituto Colombiano Agropecuario

Laboratorio de Investigaciones Médicas Veterinarias

Ciudad Universitaria, Bogotá, D. E.

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Introduction

The majority of the research and training on the bovine hemotropic diseases, anaplasmosis, babesiosis and trypanosomiasis, described in this condensed, summary report was performed at the Veterinary Medical Laboratory of Research of the Colombian Institute of Agriculture (ICA) in Bogotá, Colombia as well as in ICA experiment stations located at Tibaitatá, Palmira and Montería. Private farms were also used to ascertain some experiments.

In general, the hemotropic disease research was primarily concerned with studies on the isolation, purification and low temperature preservation of the infectious organisms, pathogenesis studies of single and multiple infections, investigations of the incidence and prevalence of the diseases in Colombia, the use of serologic procedures, premunition studies, chemotherapy, chemoprophylaxis, studies of the vectors which transmit the diseases, and research on the use of irradiation attenuated and adjuvant vaccines to control the diseases.

Research Results

organism, Anaplasma marginale, which causes bovine anaplasmosis, an infectious blood disease of cattle was isolated from a calf which was naturally infected by ticks on the Northern Colombian coast. The method of isolation and purification involved the use of chemotherapy (Ganaseg) and serial passage through splenectomized calves, which eliminated other contaminating organisms. The isolated organisms were maintained in calves and preserved at -79 C. in glycerinated (8.2% v/v) blood.

Babesia bigemina which causes bovine babesiosis, an infectious blood disease of cattle, was isolated and purified by rapid serial passage through 5 splenectomized calves within 6.5 days. The organisms were preserved and maintained at -79 C. in glycerinated (11.6% v/v) blood. Babesia argentina, which also causes bovine babesiosis, is now in the process of being isolated by the use of a modified tick transmission method and differential chemotherapy.

Trypanosoma vivax which causes an infectious blood disease of cattle, bovine trypanosomiasis, was isolated by passage through adult sheep and then through calves treated 12 days with oxytetracycline. The organism was maintained in calves and sheep.

A study of the pathogenesis of bovine babesiosis caused by B. bigemina, was performed on 15 experimentally infected calves. The clinical data indicate that the calves lost weight, had fever and were anemic. The results of the clinical pathological study disclosed the facts that some of the methods employed could be used for diagnosis and prognosis of the status of infected cattle. The data obtained from the pathological studies indicate that the organism does cause certain lesions which are characteristic of the disease and are beneficial in understanding the mechanism of bovine babesiosis.

In the field, it is known that bovine anaplasmosis and babesiosis frequently occur in Colombia as a concurrent infection. A study of the pathogenesis of the dual infection is now in progress and indicates that the severity of the dual disease may be much more pronounced than a single infection.

Because little was known about pathogenicity and virulence of Trypanosoma vivax which causes the infectious blood disease of cattle, bovine trypanosomiasis, a pathogenesis study was performed which showed that T. vivax is very pathogenic and is capable of causing a high mortality rate. The clinical studies disclosed the fact the calves had temperature, weight loss and became anemic. The clinical pathological data demonstrate that the effect of the organism on cattle can be ascertained to give a diagnosis and prognosis. The pathological lesions produced by T. vivax were characteristic and elucidated some important information on the basic disease mechanisms of bovine trypanosomiasis.

The incidence and prevalence of bovine anaplasmosis, babesiosis and trypanosomiasis in various parts of Colombia were studied by the use of serological techniques, thick and thin blood smears and blood droplet methods. An attempt is being made to draw a map of the areas where these diseases occur. Also, inoculations of bovine blood samples from various areas of Colombia into susceptible calves were used to isolate the organisms from the different zones.

Antigens were made from B. bigemina, which were employed in the complement fixation test for the serological diagnosis of bovine babesiosis in Colombia. The antigens are being studied by various methods, i.e., gel precipitation, immunoelectrophoresis, column chromatography, etc. The thick

and thin blood smear technique was used to aid in the diagnosis of bovine babesiosis.

Premunition techniques, which involve the inoculation of virulent organisms followed by chemotherapy, were studied utilizing various drugs at different dosages. An attempt was made to premunize calves against anaplasmosis and babesiosis simultaneously. Control of gastro-intestinal parasites, were also attempted. The results of following experiments are summarized in the sequence that they were executed. Four drugs were used in the experiments; Burroughs-Wellcome compound 4A65 is effective against anaplasmosis and babesiosis, Burroughs-Wellcome compound 356 C 61 and oxytetracycline are effective against anaplasmosis only, Ganaseg is effective against babesiosis only. In each of the experiments, the following parameters were measured; mortality rate, weight gain, packed cell volume, parasitemia and complement fixation. The use of 4A65 (1.0 mg/kg SQ) and 356 C 61 (5.0 mg/kg IV) 5 days following inoculation of virulent A. marginale, B. bigemina and B. argentina apparently caused sterilization and was not useful for premunization. The second approach involved the use of the same drugs and dosages, however, 4A65 (1.0 mg/kg SQ) was given once on 8, 9 and/or 10 days and 356 C 61 (5.0 mg/kg IV) was given once on 19, 20 or 21 days following injection of virulent A. marginale, B. bigemina and B. argentina. The idea being to give the organisms more time to proliferate before treatment. 4A65 was effective for the control of babesiosis, but 356 C 61 was not effective for the control of anaplasmosis and had to be repeated several times due to relapses of the infection. Therefore, the third approach was to use the same dosage and day of 4A65 treatment, but to use a single inoculation of oxytetracycline (1.2 mg/kg IV) on 19, 20 or 21 days following

inoculation of the organisms. The use of oxytetracycline was not effective, because severe relapses of anaplasmosis occurred. The fourth approach was to use Ganaseg (1.5 mg/kg IM) on day 8 and a combination of 356 C 61 (5 mg/kg IV) and oxytetracycline (12 mg/kg IV) on day 21 following inoculation of virulent A. marginale, B. bigemina and B. argentina. Excellent results were obtained in that the organisms were inhibited, but did proliferate and the calves were immune upon challenge. Finally, the use of the above mentioned 4th approach is being used in a field trial on the Northern Colombian Coast, but was modified by using Ganaseg (1.0 mg/kg IV) on day 10 or 11 and 356 C 61 (5 mg/kg IV) in combination with oxytetracycline (12 mg/kg IV) on day 21 following inoculation of virulent A. marginale, B. bigemina and B. argentina. The results of this experiment are not complete, but favorable results have been observed thus far. The Northern Colombian Coast project also incorporates tick and gastro-intestinal parasite control programs.

Compound 4A65 (1.0, 2.0, 2.5 mg/kg IM) was used to treat simultaneously acute bovine anaplasmosis and babesiosis and was very effective in the treatment of babesiosis, but was found to be only slightly effective against anaplasmosis. Compound 4A65 (2.5 mg/kg IM) at 5 or 10 applications completely sterilized against babesiosis, but did not sterilize against anaplasmosis. Ten applications of 4A65 (2.5 mg/kg IM) caused death in 5 of 6 calves.

Compound 4A65 (2.5 mg/kg SQ) was used chemoprophylactically and was very effective against blood-borne as well as tick-borne babesiosis, but was not very effective against anaplasmosis.

In regard to the tick vectors which transmit bovine anaplasmosis and babesiosis, Boophilus microplus was found to be the major vector. Dermacentor nitens, and Amblyomma cajenense were frequently recovered from Colombian cattle,

but their vector status remains unknown. Attempts are being made to isolate non-infected B. microplus ticks as well as producing B. microplus ticks with known infections of B. bigemina and B. argentina. Different insecticides have been used to control the tick populations with successful results.

Attempts were made to use a killed Babesia vaccine with and without an adjuvant. Limited success has been obtained in the field. The use of the Diamond Laboratories attenuated live A. marginale vaccine in young calves gave very little protection under tick field challenge.

Studies on the use of an irradiation attenuated Babesia bigemina vaccine are now in progress and the data indicate that dosages of 48 Krad or higher stopped the proliferation of the organism in the bovine host. Preliminary interpretations of the immunity afforded by a single application of irradiated organisms appear encouraging.

Training

Participation in the training of veterinarians has consisted principally in the direction and counseling of 13 post-doctoral students working toward either a degree of Master of Science or Doctor of Philosophy in Veterinary Microbiology or Veterinary Pathology. The names of the students are listed alphabetically as follows: Drs. Adolfo Arboleda, John Bishop, Fernando Botero, Donald Corrier, Charles Daley, Wilson Ferreria, José Hernández, Floyd Jones, Fernando Lozano, Héctor Muñoz, Jaime Payán, Kenneth Thompson and Otoniel Vizcaíno. Five of the students have completed their respective degrees and 3 other students should complete their degrees within the next 3 months. The subject of the majority of the theses was related to problem-solving research on blood diseases of cattle and was applicable to our program. Also, the Texas A&M University in Colombia has been responsible for the "in laboratory" training of 5 Colombian veterinarians and several technicians in the field of hemotropic diseases, as well as giving various seminars to professional groups in Colombia, Perú and Guyana.

Research Utilization

Anaplasmosis - Babesiosis

The acute need for answers to the questions and problems associated with hemotropic diseases has resulted in rapid utilization and acceptance of research findings; in some instances even before the final conclusion of controlled laboratory experiments.

The survey made of these infections in Colombia has clearly identified the problem areas, as well as the clean areas where these diseases do not occur. The correlation of Anaplasma incidence with various climatic zones reveals a pattern which would provide valid information to all parts of Latin America.

Research has clearly indicated that premunition is the method of choice at the present time to prevent clinical anaplasmosis and babesiosis in Colombia. This information is being utilized in present field trials currently underway at Turipana.

The synergistic effects of combined drug therapy first detected at Texas A&M only a few months ago is currently in use in Colombia as a treatment to moderate Anaplasma premunizing infections. One treatment with the combined drugs is equivalent to 4 injections of the previous therapeutic agent. Progress is continuing in this area of research.

Similar progress has been made with a new drug for Babesia. This drug has been found to be more effective, even to the point of entirely removing infection, which in some instances is not entirely desirable. The use of premunition has under controlled conditions shown real value in eliminating

deaths in cattle moved into endemic zones, and the techniques developed for premunition have been shown to be safe.

A large number of facts have been revealed recently concerning basic characteristics of these disease agents, which while not being utilized directly by the livestock producer, or the practicing veterinarian, are being utilized as stepping stones on the way to field application.

This and other information is being made available to scientific workers in this field through the normal channels of publications. A list of current publications is presented at the conclusion of the 1971 technical annual reports. Since the inception of the Institute of Tropical Veterinary Medicine in 1967 there have been 26 publications in scientific journals, dealing with hemotropic diseases and 17 papers presented at scientific meetings, as the result of work by 3 full time Institute staff members. During this period 234 reprints (from 1 staff member only) have been mailed out at the request of scientific workers in the U.S. and 26 foreign countries.

In addition to these more routine communications our annual reports (pre-publication) have, on request, been sent to numerous colleagues working on similar problems. Some current contacts of those groups and individuals that have requested our reports, technical assistance and cooperation include:

(1) Centro Internacional de Agricultura Tropical Colombia.

(2) Delta Regional Primate Research Center, Tulane University (Dr. F. Hawking).

(3) U.S. Naval Medical Research Unit No. 3, Medical Zoology Department Cairo, Egypt.

(4) Royal (Dick) School of Veterinary Studies, Centre for Tropical Veterinary Medicine, University of Edinburg, Scotland.

(5) Centro de Investigaciones Veterinarias, Ministerio de Agricultura y Cria (W. F. Schroeder), Venezuela.

(6) Department of Tropical Veterinary Science, James Cook University of North Queensland, Australia. (Philip Ladds).

(7) Veterinary Diagnostic Laboratory, Ministry of Agriculture Port of Spain, Trinidad (M. W. Smith).

(8) U.S.D.A. - Entomology Research Division, Kerrville, Texas (O. H. Graham).

(9) East African Veterinary Research Organization, Muguga, Kenya (G. Corry).

(10) School of Veterinary Medicine, University of Caldas Manizales, Colombia.

(11) Instituto Colombiano Agropecuario Bogota, Colombia.

(12) University of San Marcos, College of Veterinary Medicine, Lima Peru.

(13) Burroughs-Wellcome Laboratories.

(14) Diamond Laboratories, Des Moines, Iowa.

Institute staff have received numerous professional visitors over the past few years, who have expressed interest in our research findings, and who have taken with them copies of our reports, for use in their own areas.

It is impossible to identify all aspects of research utilization, and in areas of primarily basic research it is even more difficult for research results to be put to immediate use in achieving the goal of increased food production, but in all probability the urgent need, for

information in the area of hemotropic diseases will see even more rapid utilization of the technology being developed, than is normally encountered.