SEMINAR PROCEEDINGS

"Future prospects on Vaccine Production Technology"

INTRODUCTION

A Seminar was held on January 21st, 2000 to commemorate the completion of the project to Develop Produce and Control Human Rabies Vaccine on a VERO cell substrate. The meeting was met in Bogotá, Colombia, with the participation of some of the scientists that collaborated on the project. The objectives of the meeting were to review a short history of the project, some highlights of the technology, major aspects of the design and physical characteristics of the installations, control procedures and results, and the outcome of the field trial in human volunteers.

The Seminar was preceded by an official inauguration of the facilities with the attendance of government officials, representatives from the World Health Organization, Panamerican Health Organization, Pasteur Institute, Rockefeller Foundation, former members of the Rabies Group of Experts, and private consultants. The major goal of the Seminar was to obtain comments on the VECOL's INMUNOVAC vaccine and the technology, and to formulate proposals for improving the use of the vaccine and it's application. Another objective was also to discuss possible future uses of the technology for other products or vaccines.

PROGRAM

A.M.

8:00 Opening Remarks
Juan Esteban Restrepo S.M (Vecol S.A)
Jorge Boshell (INS)
Primo Arambulo III (PAHO)

8:30 Historical perspective
Scott Halstead (Consultant)

9:10 Technology design, characteristics
Pierre Trepanier (Consultant)
and Plant Facilities
Joan McMahan (Consultant)
Eduardo Aycardi (Vecol S.A.)

10:30 Coffee Break

10:50 Field trial on human volunteers
Jorge Boshell (INS)

11:15 Quality assurance
Adriana Sierra (Vecol S.A.)

11:40 Rabies epidemiology, vaccines,
Francois Meslin (WHO)
current status
Primo Arambulo III (PAHO)
Henri Tsiang (Pasteur Institute)

12:45 Break
P.M

2:20  Round Table Discussion
Future Prospects
Representatives: INS, WHO, PAHO, IAF BIOVAC, PASTEUR, VECOL.
Chair: Scott Halstead
3:30  Break
3:50  Discussion
5:30  Summary

DEVELOPMENT OF THE SEMINAR

A brief introduction by the General Manager of VECOL, Juan Esteban Restrepo S.M. was given. He welcomed the participants and gave best wishes for the success of the meeting. He also asked for recommendations that could be of use to VECOL for developing a marketing strategy for the vaccine within Colombia as well as in other countries.

Dr. Jorge Boshell, Director of the National Institute of Health of Colombia (INS) made introductory remarks praising the efforts for the development of the vaccine and the project, and stating that the trial on human volunteers was completed successfully with good protection afforded by INMUNOVAC.

The Director of Public Health from PAHO, Dr. Primo Arambulo III, made opening remarks explaining the roll of his organization for the improvement of vaccine quality for the products to be use in different countries of the Western Hemisphere to control rabies in the human and animal populations.

The first paper was presented by Dr. Scott Halstead, adjunct professor, Department of Preventive Medicine, Uniformed Services University of Health Sciences, Bethesda, MD, USA. His talk was titled "A Short History of the RF/WHO Rabies Vaccine Production Technology Transfer Project ". In his paper he described the initiation of the project in 1986 with the screening of several countries to receive and develop a new production technology based on the micro carrier technology originally described by Antoon L. Van Wezel in the Netherlands and improved by Dr. William Thilly from MIT.
He described many of the obstacles that faced the program and the rationale behind WHO involvement. He emphasized several important secondary benefits of the production of a tissue culture viral vaccine. Of
importance were that the same production unit, the same personnel, equipment, and basic supplies and services could be use for producing veterinary and human vaccines with shared benefits for human health and improved food production. Another benefit is the development of basic techniques for assessing safety and efficacy testing of biologics quality control. In short he emphasized the needs in many countries for an inexpensive yet potent tissue culture-based rabies vaccine.

Dr. Halstead related that some of the delays in the completion of the technology project were due to the death of A.L. Van Wezel, the privatization of the Institute Armand Frappier and the execution of the field trial in human volunteers, and subsequent laboratory testing. He also paid tribute to the deceased Raymond McMahan for his contribution to the project. He examined some of the broader questions raised by the conclusion of this project since rabies has never risen to a high priority on the list of vaccines for distribution to developing countries prepared by WHO, UNICEF and other global vaccine proponents. He stated that INMUNOVAC, the VECOL's rabies vaccine, joins an elite list of high quality biologicals that can be expected to serve the needs of human beings for generations to come.

The second paper was delivered by Dr. Pierre Trepanier a former member of the Biovac team in Montreal and now acting as a consultant for the group. He described the collaboration that existed before the start of the project between their group and the MIT group headed by Dr. Thilly. He mentioned the initial steps used a high-density cell culture for the cultivation of polio-virus. He described the methodology to develop a highly efficient media for culturing Vero cells and producing rabies virus, including experiments to obtain an efficient system for concentration and purification of the virus.

He mentioned the efforts to develop process controls especially designed to quantitate viral production. ELISA tests were used to measure the amount of glycoprotein present in the cultures using monoclonal antibodies. They were obtained from a Hybridoma from the Center for Disease Control (CDC), United States. Some of the work done related to the measurement of the residual cell DNA in the final harvest. Mention was made of the training of four people in production development and four people in quality assurance (two from VECOL and two from INS).

He described the complicated work related to the concentration and purification steps needed to obtain a pure virus for formulation. Many trials had to be conducted with different systems until a one step chromatographic procedure was standardized and DNA content examined to guarantee its removal to meet the recommended WHO level.
The following paper was given by Dr. Joan McMahan, President of M&M Consultants, Fla. USA. She served as a consultant for major parts of the program. She described in detail some of the physical characteristics of the design of the Production Plant including the air handling system. She emphasized that much of the knowledge for production and development was already at VECOL before the start of the project, especially related to virus handling, fermentation, recovery, sterility concepts, water, steam and air quality and several others. She also mentioned some of the development inputs that the team at VECOL made for the program. A special consideration was made for the development of master and working cell and virus banks, viral concentration, multiplicity of infection, animal testing, viral formulation, additives for freeze drying, lyophilization, stability, DNA quantification, production of monoclonals, and measuring glycoprotein content, quality control testing and standards, design and validation to comply with GMP's and standard operating procedures.

She mentioned that the project could never have happened without a team effort at VECOL and that VECOL's contribution has not only been technological, but that they heavily invested in the physical facilities, labor, as well as equipment, such as the specially design New Brunswick fermentors.

She also made a point of the strong effort made to comply with good manufacturing practices and described with pictures the different areas for the production of media, cells, virus, purification, filling and freeze drying of ampoules. Dr. McMahan congratulated VECOL and it's scientific staff for the successful completion of this important project.

Dr. Eduardo Aycardi, VECOL's Research and Development Manager, described some of the basic components of the production technology assembled, researched and standardized by the company. Main emphasis was placed on the special and proprietary design of the decanting column for the New Brunswick fermentor developed in collaboration with Professor William Thilly from MIT and NBS scientists. With this technology Vero cells would produce virus up to 25 days in the fermentor with continuous flow of media and viral harvest. Other major components of the technology include compositions of the media for cell and virus growth, high-density micro carrier cell culture, concentration and purification steps, and the final formulation of the vaccine. Concurrent with the basic production technology several process control techniques were developed and will be described in another paper.

A description was given of the use of the vaccine and recommended schedules for immunization. Emphasized were the principal advantages of
this cell culture vaccine, namely, the innocuity achieved by the purification procedure and absence of proteins in the final product.

In summary, the rabies vaccine that VECOL is offering for the public health campaigns is unique in many respects. It complies with international standards and is without doubt the only one in Latin-America with high concentration and purification.

Dr. Jorge Boshell Director of the National Institute of Health of Colombia (INS), in relation to the field trials, explained the design of an immunogenicity study to evaluate the efficacy of the VECOL's Vero cell vaccine. He described a study conducted on fifty-nine volunteer veterinary students from a local University, ages 22 - 26, with no previous rabies vaccination, and no evidence of immunodeficiency. Students were vaccinated on days 0, 7 and 30, and bled on days 0, 15, 30 and 45. They concluded that INMUNOVAC gave satisfactory protection 7 days after initial vaccination (antibody content of 2.5 IU / ml in average, as compared to a requirement of 0.5 IU / ml). Equally gave excellent protection at 30 days (antibody content of 3.3 IU / ml). He also described the evaluation of secondary effects of the vaccine on the students and concluded that they were negligible.

In summary the vaccine affords very good protection at 15 and 30 days post-vaccination with no detectable secondary effects.

Dr. Adriana Sierra from the VECOL's staff and at present in charge of the Rabies Production Unit gave the next presentation on quality assurance. She described the principal components of quality assurance both at VECOL and at the Food and Drug Administration of Colombia (INVIMA). Main emphasis was given to sterility, innocuity and potency tests for the final product. This last analysis was carried out in comparison to the Fifth International Vaccine Standard obtained from the Staten Serum Institute from Denmark and approved by WHO. A National reference standard was prepared for this purpose. She also explained the physical and chemical analysis performed on the freeze-dried final product and on the vaccine diluent.

An important consideration was given to the measurement of residual cell DNA in the vaccine. It is far below the recommended level established by WHO for cell derived vaccines. Another factor that received particular attention was the study made to compare the viral content as measured by mouse intracerebral titration with the glycoprotein content measured by an ELISA test. Monoclonal antibodies were used harvested from Hybridoma cells of a bank, donated by the Center for Disease Control (CDC), USA. The hybridoma cells were cultured and then inoculated in
mice to obtain ascitic fluid. This was clarified and purified to obtain monoclonal antibodies anti-glycoprotein for use in the ELISA test.

In conclusion, the tests performed on the principal vaccine components, cells and virus gave satisfactory results and guaranteed vaccine quality. Likewise the analysis performed on four pilot lots gave satisfactory results, both at VECOL and at reference laboratories, and guaranteed consistency in quality assurance.

The following presentation was by Dr. Francois Meslin, Team Coordinator of the Animal and Food Related Public Health Risks, World Health Organization (WHO), Geneva, Switzerland, who described the importance of human rabies in the world with the following examples: every 10 to 15 minutes someone dies from rabies in the world; a thousand people receive rabies post-exposure treatment every hour in the world, and in most instances a dog is at the origin of the exposure. Today only 50% of the post-exposure treatments applied world wide are completed using vaccines produced in tissue culture, the rest are vaccines produced in animal brains.

He described the major constraints to rabies control and elimination in developing countries. The main is the shortage of affordable, safe and effective rabies vaccines and immuno-globulin for post-exposure treatment, lack of rabies diagnosis and surveillance, and non-sustainable national dog rabies control measures. This last activity is due to the lack of collaboration between the Health and Veterinary Sectors in the countries involved.

He mentioned the WHO Rabies Vaccine Initiative 2000 as an effort to overcome the current lack of affordable and safe rabies vaccines for humans by identifying and agreeing on strategies for use of modern vaccines; facilitating imports of rabies biologicals to countries in greatest need; increasing adherence to Standard Operating rocedures (SOP) in rabies vaccines management; modern vaccines and immunoglobulin production and application in rabies-infected countries, especially in Africa and Asia; fostering projects for the complete or partial transfer of technology for the production of modern rabies vaccines.

He concluded there is an increase in rabies infection in developing countries with an estimate for the dog rabies infected areas close to 70,000 human deaths and 8,000,000 human post-exposure treatments in Africa, Asia and the Americas combined.

Dr. Primo Arambulo III, Regional Coordinator Veterinary Public Health, Panamerican Health Office (PAHO) in Washington, USA, gave estimates on the availability of rabies vaccines for the human and animal population
in the Americas. He described the production of rabies vaccine prepared in suckling mouse brain in Latin-America with a current total estimated production of 3.850,000 doses.

He emphasized the importance of replacing worldwide the suckling mouse brain derived vaccine for the more modern tissue culture based vaccines. The figures for the number of doses of this last group of vaccines used in the region are estimated at 1,000,000 in total. Dr. Arambulo made a point of the importance of dog vaccination as a means to control the need for human vaccination. He noted that in the last few years the countries have eliminated roughly 800,000 dogs annually and have applied close to 34,000,000 doses to protect the canine population in the Americas.

The last presentation in the morning program was given by Dr. Henri Tsiang, Head of Rabies Unit, and National Reference Center for Rabies, Pasteur Institute, Paris, France. He spoke about the important characteristics that a reliable rabies vaccine should have, such as, decreased side effects, and concentrated and purified virus to diminish the number of applications. Mention was made of the different attempts to produce newer vaccines for rabies. Many studies have been conducted using the extracted glycoprotein from the virus in synthetic membranes and genetically engineered vaccines with recombinant techniques. Other fractions such as poly-peptides and macro-encapsulation procedures have been tried with limited success. Recombinant vaccines using vaccinia vectors, canary pox virus, and procariotic gene expression vectors to express the rabies glycoprotein using yeasts, E. Coli, Baculovirus, and even plant viruses as vectors have received considerable research attention, but there is no practical use as yet of any of these technologies.

More recently research has been underway to use DNA vaccines. Rabies vaccine production attempts have been made using Eucariotic vectors and Adenoviruses with promising results when given by the intramuscular route. However, much work has to be done in order to use these vaccines in a practical or industrial manner. His main conclusion was that the tissue culture based rabies vaccines will be the main choice for eradication of rabies in the human population for many years to come.

ROUND TABLE DISCUSSION

The discussion was initiated by Dr. Halstead explaining the importance of rabies and the use of vaccines as a treatment after exposure. This is the only vaccine that has this particular use. He gave consideration for the vaccines that have been traditionally prepared in government laboratories and the fact that in many developing countries these vaccines are given free to the general population. Hence, in many countries people are not used to paying for vaccines, but will pay up to US$25 or even more for an
antibiotic or pharmaceutical. A strong effort must be made to spread the knowledge in the general public to appreciate the real value of vaccines and the importance of preventive measures to avoid infectious diseases.

He asked for comments on the marketing of INMUNOVAC, and for recommendations by WHO and PAHO with respect to the vaccine insert, and also on the possible sale of this vaccine to neighboring countries. He also asked for recommendations on the use of immuno-globulin to be given simultaneously with the rabies vaccine injections.

Dr. Meslin (WHO, Geneve) gave his comments on the vaccine insert. He recommended to not include the subcutaneous route, but only the intramuscular application since the vaccine has only been tested by this method. He made clear that the OMS recommendation, for pre-exposure application of rabies vaccine, is three doses on days 0, 7 and 28. They do not have a firm recommendation for additional booster doses, but it is generally accepted that they could be given on a yearly basis, unless a protective serum titer could be assessed on an individual basis. He also gave his comments on WHO recommendations for post-exposure treatment. They have at least five recommended schedules, the most commonly used being the Essen Treatment, using five injections on days 0, 3, 7, 14 and 30. Other reduced schemes using two doses on day 0 and boosters on days 7 and 21. Additional variations could be recommended but can not be placed on the insert unless they are tried with this vaccine.

He also mentioned several schemes using the intradermal route of inoculation. They have given good results especially in Asia; that could be tried with this vaccine. He also commented on the repeated exposure of a person that has received the post-exposure treatment, and was exposed to rabies virus again. In this case WHO recommends two booster doses on days 0 and 3 and not one dose if the person has received vaccination during the previous year or three doses if the previous vaccination was more than a year before, as specified in the insert.

Dr. Raúl Londoño from PAHO, made some comments afterwards with respect to vaccination schemes. He agreed with Dr. Meslin in many respects but suggested to add in the insert, that in case of an overwhelming exposure to rabies, the person should receive an immunoglobulin shot, depending on the degree of exposure, the extent of the lesion and other epidemiological considerations.

Dr. Londoño also commented on a possibility of marketing the vaccine mainly through governments similarly to what has been done in Guatemala. They are importing rabies vaccines for human use without health registration in the country. He emphasized that to assess the number of treatments needed for the American Continent we must consider the number of deaths in the region. That was close to 78 cases
last year, but we have to talk about 500,000 treatments used during the same period of time. If we also consider that there is only 30% notification, we then are talking about 3.5 million treatments for the rabies exposed population that need a high quality and reliable vaccine.

The Chair asked for assistance to convey the recommendations on the insert to INVIMA (Colombian FDA), since he sees no representative of them at the meeting.

Dr. Aycardi commented that INVIMA does not have a special regulation on the insert for rabies vaccine. The recommendations from this meeting are compiled and the insert changed accordingly. A new insert is submitted to INVIMA for approval.

The Chair explained that in several vaccines available in the U.S. they include long inserts with much detailed information for vaccine usage. In this case they probably include all WHO recommendations and their own. The general accepted procedure is to include only procedures that have been tested with any particular vaccine.

Dr. Meslin made reference to his suggestions of using WHO recommendations and insisted that in the insert reference could contain the national equivalent of the FDA in each country. But if we choose WHO recommendations we should probably make reference to this in the insert. He also made a point of insisting in the need of conducting a post-exposure trial using human volunteers with five vaccine injections. He made reference to previous conversations during the meeting where some people argued that if the vaccine gave excellent results with 3 doses, as shown by INS with the field trial, there will be no need to run a test with 5 doses. However in order to have a scientific basis to recommend this vaccine for post-exposure treatment, actual real data from a study must be shown.

He also mentioned that some commercial houses and laboratories make reference frequently to WHO recommendations. However, some of the larger producers do their own studies which have inspired WHO proposals.

The Chair added that in summary we should not develop any specific recommendation for people that have been vaccinated and exposed, and that we should continue recommending two doses on days 0 and 3 following the WHO recommended schedule.

Dr. Meslin explained that a group in Vietnam is conducting some trials using the intradermal route of injection with a new protocol. They are using volunteers mainly from veterinary schools with a complete risk assessment. They were given a complete post-exposure treatment, even
though they were not exposed to rabies virus. This made sure that the only adverse effects that could appear would be local reactions.

The Chair asked for comments on the status of determining the price for the new human vaccine.

Dr. Aycardi from VECOL explained that the strategy for determining the price for the new product is very complex. Many factors have to be taken into consideration such as volume of product, mode of use, entity that is buying the product, discounts for mode of payment, volume and many others. What VECOL is requesting is a comparison with the existing Suckling Mouse Brain (SMB) products in the market; many of these products are given free to the end user by government institutions. In essence VECOL will have to fix a price that is not too low, considering unfortunately, that it is viewed by general opinion that any cheap product is of low quality, and low enough to compete with cell derived vaccines already in the market.

The Chair requested comments from the Ministry of Health on the current price for the SMB vaccine. A representative from that institution informed that the current price is US $1 per dose, and the recommended treatment is 7 doses. They produce a box with 7 ampoules for the total treatment. This price is paid by the Ministry of Health to the INS that produces the vaccine. The shelf life of the vaccine is only 18 months.

The Chair exchanged some views with Dr. Arambulo from PAHO, on how to settle the price for the new vaccine considering that there are similar products on the market. That clearly we should make a difference for the new product as far as benefits are concerned. This is in effect to develop a marketing strategy.

Dr. Tom Yuill, from the University of Wisconsin, expressed the view that the price depends more on who is the principal buyer. As far as we know governments are the main clients for the vaccine. A very important consideration they have to understand is the advantages that the new vaccine offers as compared to the older SMB vaccines.

Dr. Henri Tsiang, from the Pasteur Institute, commented that from his point of view there are two major challenges for the new vaccine. One is to convince the Colombian government and other governments that this is the appropriate vaccine to combat rabies in their region, and this is the first priority. In the long run we have to demonstrate a scientific environment to convince governments that the new vaccine is actually cheaper, better and the best choice for a reliable control of rabies. To do that, a study should be undertaken to run comparative studies for the
protective activity afforded by the vaccine against different viral strains, for example the Lysa Virus.

The next comment was made by Dr. Arambulo. He said that the vaccine price varies considerably, not only from vaccine to vaccine, but also from country to country and more so depending on who is the buyer. He does not understand why a vaccine shot cost roughly US $100 in the US, while the same product is only US $20 in France. In general, for the cell derived vaccines, some developing countries are paying US $8 per dose, and there are some countries and Ministries of Health that are buying the same vaccine for US $2.50. However, in this last case they are probably receiving something else in exchange for this low price.

Dr. Arambulo added that PAHO is buying rabies vaccine for some countries in the Americas. They rely on the requirements of each country for either the brain derived vaccine or the cell culture origin vaccine. Some countries have both vaccines available readily within the country. Other countries depend on the possibility of getting the vaccine within 24 hours from a Miami distributor. Even though prices vary considerably, PAHO is buying amounts from over 90,000 doses at US $9 per dose, from 20,000 to 90,000 doses of rabies vaccine for US $10 per dose, and less than 20,000 doses for US $11 per dose.

The Chair asked for comments in relation to the requisites required by PAHO to order vaccines from different suppliers.

Dr. Arambulo explained that PAHO currently does not buy directly from the Washington office; rather they expect each representative in their respective country to buy their own needs. They require in each case a quality control certification.

The next consideration was that vaccines that are intended for use in Foot and Mouth Disease free countries should be produced also in FMD free areas. As far as rabies vaccine on diploid cells, PAHO is buying the vaccine on request from several countries through a special deal at a price below the market level, from a Miami office. They can deliver it to Central or South America within 24-48 hours.

A question was asked if the restriction for the veterinary products applies equally to human vaccines. Dr. Arambulo answered explaining that all the products of animal origin for human or animal use coming from FMD infected countries, are prohibited to enter FMD free countries. This includes vaccines, sera and reagents. When FMD invaded Peru, even the importation of asparagus and mushrooms were prohibited for these agricultural products going from Peru to Chile.
Dr. McMahan asked how Argentina has been exporting meat derived products to US considering that they have not been declared free of FMD yet. Dr. Arambulo explained that only in the last 3 years FMD free areas within a country have been recognized. A region in Argentina for example, was declared officially free of the disease two years ago. From this point on, they were able to export frozen beef to US. By the same token, if VECOL produces the rabies vaccine in the free area of Choco they could export it from there to FMD free countries.

When the Chair asked for additional comments, Dr. Meslin said the following: “I'm going to read you excerpts from a WHO document that I did not even know existed in relation to the quality of vaccines bought by WHO. What they really do is to make an evaluation as far as requirements to advise UNICEF and other UN agencies for vaccine approval. In essence this document which I am going to leave for reference, asks for 12 points to describe the vaccine in detail, the internal and external testing, the protocols for 5 consecutive lots, and then to send samples to WHO collaborative centers to be examined for compliance to WHO requirements. The written and laboratory reports are sent to UN agencies interested in buying vaccines for the regions. An important consideration is that WHO guarantees the confidentiality of this information, which is not revealed under any circumstances. WHO sends a team for a visit to the laboratories interested in exporting the vaccines to verify the conditions described in the documents.”

The Chair asked for information on the number of doses bought directly from WHO. To which Dr. Meslin reply that they only buy small amounts for different areas. However he remembers that UNICEF bought close to half a million doses of vaccine for Tanzania, but this does not occur regularly.

Dr. Halstead express his opinion on this matter explaining that rabies is not on the priority list for the major donor agencies. However some day it might happen. Dr. Arambulo added some comments explaining that when there is vaccine surplus, countries like Brazil donated SMB vaccines to other countries when they have in excess of their internal needs.

When asked for additional comments, Dr. Londoño explained that due to the globalization, countries are buying vaccines depending on quality and price with exception made for the production in the government owned laboratories, in the Ministers of Health or Agriculture, at prices that are very difficult to asses.

Dr. Halstead summarized some of the recommendations emphasizing that there is a need for scientific publications on vaccine evaluation in addition
to the studies already performed and newer well design field tests. This is
difficult work but the only way to support the immunity claimed.

Dr. Tsiang made a comparison of the four pilot vaccine lots prepared by
VECOL noting that only one had an NIH result of 9 International Units, the
other three were in the range of 3 units. He suggested that in order to
compete in the market, VECOL's vaccine average NIH testing result
should be around 7 or 9 units.

As far as the size of the market, Dr. Arambulo said that according to the
statistics in the region there is a need of close to 1 million human doses,
and even more. The main challenge for the VECOL's vaccine is to
displace the SMB (Fuenzalida) vaccine. If any laboratory markets a cell
derived vaccine at a price competitive with the SMB vaccine, the SMB
product will be displaced rapidly.

Dr. Meslin made the next comment on this topic. He is of the opinion that
VECOL could sell the Vero based vaccine for a price higher than the SMB
vaccine considering that there are additional guarantees as far as quality
and safety, and that the numbers of applications are diminished. In this
same context Dr. Londoño added that these two vaccines should not be
compared on the basis of the price of each dose, but rather on the total
price of the complete treatment. The best comparison would be to
calculate all the medical expenses incurred for the protocol using the SMB
vaccine of 7 to 14 doses. This would have to be compared to the Vero
vaccine protocol of 3 to 5 doses with much less medical expenses and
even less total cost. In the working hours lost by the patient visiting the
health center for vaccinations and controls have to be considered.

Another way to reduce costs, explained by Dr. Meslin, is to implement the
intradermal route of inoculation using a reduced dose in size. However, it
was argued that a more specialized health team is needed for this
procedure. They have to be trained specially to perform a reliable
application. This is true in spite of the fact that most treatments are
given at Health Centers even in developing countries. In any event it is
an alternative that could be tested and implemented in special cases.

The Chair asked for comments on the use of immunoglobulins additional
to the application of the vaccine. Dr. Meslin said that the WHO
recommendation is to use immunoglobulins in all category 3 rabies
exposures. The main constraint for using these recommendations in
developing countries is the cost, since each globulin dose amounts to
approximately US $25 and two doses are needed. Hence you have to add
US $50 for each protocol, and it is not affordable in most cases. Another
option recommended by WHO, is to substitute the immunoglobulin for an
intradermal application of vaccine using 8 doses simultaneously in
different parts of the body. This has given good and quick immunity for post-exposure treatments of category 3 exposures.

With these comments the chairman declared the session closed.

Dr. Juan Esteban Restrepo SM from Vecol thanked the participants for their collaboration, support and recommendations and remarked that they will be studied in detail for implementation. The meeting was adjourned.

FEBRUARY, 2001
BOGOTA, COLOMBIA
VECOL S.A.