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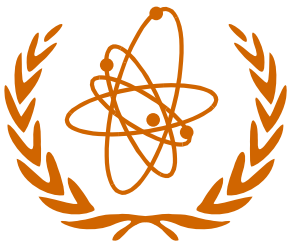

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SECTION A – NEWS

CONFERENCE REPORT

The 26th ISCTRC Conference was held at Ouagadougou, Burkina Faso, 1-5 October 2001. Given below is an edited summary of some of the draft reports and recommendations of the Conference. Other contributions to the conference will appear in later issues of *TTIQ*.

OAU: administrative structures and developments

The OAU Heads of State and government during their summit in Lomé, Togo, in July 2000 and, subsequently, in Lusaka, Zambia, in July 2001 declared a campaign for the eradication of tsetse flies from the continent of Africa. This action follows on the recommendations of the 25th ISCTRC conference and recognises the hardships that tsetse and trypanosomiasis impose on the livelihood of rural communities in sub-Saharan Africa. The Secretary General of the OAU was instructed to supervise the tsetse eradication campaign and national governments were called upon to include tsetse eradication in their respective national development plans.

A Task-force of twenty two people appointed by the OAU Secretary General met in Nairobi, Kenya in December 2000 and developed a conceptual framework and a short-term action plan of the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC). This was endorsed at the Lusaka OAU Summit in July 2001 and a co-ordinator has since been appointed and temporarily posted at the OAU Headquarters, Addis Ababa, Ethiopia.

OAU/IBAR conducted a two day (29-30 September 2001) Orientation Workshop for Directors of Animal Resources and Veterinary Services on Policy Planning and Strategy on PATTEC Implementation in Ouagadougou, Burkina Faso.

OAU/IBAR and ISCTRC Secretariat continue to co-operate and collaborate with international and regional institutions and organizations such as FAO, WHO, IAEA, ILRI, ICIPE, PAAT and OIE. PATTEC was officially launched on Friday afternoon, 5 October 2001.

FITCA and other projects under development

With regard to project co-ordination and implementation, it was reported that Farming in Tsetse Control Areas (FITCA) was operational in Ethiopia, Kenya and Uganda. The West and Central Africa project proposal is with the EU awaiting their decision.

Pipeline projects under PATTEC Framework include the Ethiopian SIT Project, the Lake Victoria Basin project (Kenya, Uganda, Tanzania) and the ongoing projects in Botswana, Burkina Faso and Mali.

PATTEC

PATTEC, the Pan African Tsetse and Trypanosomiasis Eradication Campaign, arose from a consensus regarding the negative effects of tsetse and trypanosomiasis on the

development and welfare of rural populations in sub-Saharan Africa, and on the need to rid the affected areas of this menace. Tsetse eradication is technically feasible, and is politically and economically desirable. To achieve it, Africa should be as resolute as she was in her fight for political liberation. Scientists should identify zones that are isolated or isolable, as in the Botswana, Ethiopia, Mali/Burkina Faso SIT Projects.

African countries should act and chart out mechanisms for support and coherence. Achieving the PATTEC objectives will require great determination and support from the international community.

PAAT and its links with PATTEC

PAAT, the Programme Against African Trypanosomiasis, was formed five years ago under the three mandated UN Agencies, WHO, FAO and IAEA together with OAU/IBAR, to create an international forum in tsetse and trypanosomiasis control. It has the goal of improved human health, food security, sustainable agriculture and rural development.

The principal functions of PAAT are to provide expert advice, establish international guidelines for tsetse and trypanosomiasis interventions and related development activities, develop decision-support systems for the selection of priority areas and most appropriate strategies for interventions, increase international awareness of the problem of African trypanosomiasis in man and animals and assist in the mobilization of international support for tsetse and trypanosomiasis interventions.

An important activity over the past year has been to develop the process of harmonization between PAAT and PATTEC. This process is being developed through a series of meetings between the secretariats of PAAT and PATTEC. One of the chief functions of PAAT is to be an important supportive forum for PATTEC and provide international expertise on various aspects of tsetse and trypanosomiasis management and the associated issues of land use, environmental protection and long-term sustainable agricultural development.

FAO

The work of the Food and Agriculture Organization (FAO) incorporates, *inter alia*, the production of guidelines to promote sustainable livestock and overall agriculture production. In tsetse and trypanosomiasis control, three principles are followed: the integration and optimisation of technical tools, the integration of tsetse and trypanosomiasis control programmes into overall agricultural development, and investigating the social, economic and environmental long-term profitability of interventions. FAO held a meeting for liaison officers on tsetse and trypanosomiasis in east and southern Africa in September 2000 in Addis Ababa, and for central and west Africa in September 2001 in Ouagadougou. Workshops on Strategic Planning of Area-wide Tsetse and Trypanosomiasis Control in West Africa were held in November 2000 in Geneva, Switzerland, and in May 2001 in Ouagadougou, Burkina Faso. FAO plans to hold similar workshops, one each in east Africa and central/southern Africa, in the year 2002. FAO co-ordinates a number of PAAT activities: a PAAT secretariat meeting was held in February 2001 at IAEA, Vienna, Austria, at which PAAT-PATTEC harmonization was discussed. A document on "PAAT-PATTEC most frequently asked questions" was

produced. PAAT-Information System (PAAT-IS) housed at FAO headquarters, Rome, Italy, is composed of GIS, Bibliography and Resource Inventory, the website (www.fao.org/paat/html/home.htm), and the PAAT Newsletter. The Information System is available on CD from FAO, Rome or can be downloaded from the web (ergodd.zoo.ox.ac.uk/paatdown/index.htm). ESRI Arc View and Spatial Analyst has donated copies of Arc View 3.2 and Spatial Analyst 2.0 software necessary to operate the Geographical Information System (GIS) component of PAAT-IS. FAO is supporting a TCP project on Sustainable Control of Tsetse and Trypanosomiasis in the Sudan. It was approved in December 2000 and became operational in 2001. The first part of a study by the University of Strathclyde, on quality control of diminazene preparations in sub-Saharan Africa, was concluded; the results were presented at the 7th PAG meeting.

IAEA

The International Atomic Energy Agency congratulated OAU/IBAR and Member States on their efforts to generate awareness and commitment at the very top political level in Africa to try to solve the tsetse and trypanosomiasis problem. The political decision gave birth to the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) and Plan of Action.

The specific IAEA contributions to tsetse and trypanosomiasis control efforts include normative work and applied research under the FAO/IAEA Programme and IAEA's department of Technical Co-operation. The Agency is active in the field of improved diagnosis of the disease and the SIT component. FAO/IAEA focuses on developing, standardising and validating diagnostic methods and surveillance. IAEA collaborates closely with other PAAT Secretariat members and fully supports OAU and PATTEC in their endeavours.

The budget of IAEA TCs Department in the next 10 years is projected at about US$30 million. The funds will be allocated for support to PATTEC efforts, to upgrade existing and to establish new rearing facilities, assist national and sub-regional efforts in priority intervention zones, and to encourage other partners to support post-tsetse eradication development of livestock-agricultural systems.

ICIPE

The International Centre of Insect Physiology and Ecology congratulated the OAU Heads of State and Governments for their historic declaration and attention to this most serious problem in livestock and crop-based agriculture, namely tsetse and trypanosomiasis.

Human trypanosomiasis is taking an increasing toll on the African workforce with 500,000 cases per year. The disease is back to its levels of the 1930s. Having conducted research on tsetse and its management for over 30 years, ICIPE understands well the enormity and difficulty of the problem.

ICIPE pointed out some of the difficulties likely to be encountered with an "eradication approach". Some of these are that tsetse flies are very specialised insects well adapted to their habitat, and that there are 22 different species, each with unique behavioural and habitat preferences. This suggests that there are actually 22 problems; such great complexity might limit the effectiveness of the SIT method of control;

moreover tsetse have a remarkable ability to re-invade cleared areas. Therefore, African countries must join together to manage this menace, which knows no international borders. ICIPE, however, have serious concerns on the biological and logistical feasibility and the economics of the tactics being considered. Reaching the critical mass of man-reared tsetse will be much more difficult as tsetse have a low reproductive rate. ICIPE reckons, based on Zanzibar SIT project estimates, that to cover 10-20,000 km² will require 500,000 sterile males a week, or 24 million in a year. To achieve these figures, about 2 million producing females a week will be required. In addition, 19 tons of hygienic blood will be needed yearly to maintain such a colony. The cost of eradicating tsetse with SIT in Zanzibar (an isolated island off Tanzania mainland) was US$5.8 million. To clear the whole continent, DFID estimates US$20 billion will be needed.

ICIPE suggest that an integrated approach is the most sustainable one. It would be an approach that local communities could manage, is affordable within the limited budgets of African countries and communities and deals with all the complexities of tsetse behaviour and biodiversity. ICIPE will render support in any way to helping Africa solve this very complex and all-encompassing development issue.

ILRI

Trypanosomiasis research activities at ILRI are conducted within the broader livestock research and development context. ILRI has six disciplinary research programmes including: health; genetics; feed and nutrition; policy; systems analysis and impact assessment; and people, livestock and environment. ILRI research activities are closely linked to research activities with regional and national parties, or are partnerships with advanced research institutes in developed and developing countries.

The purpose of ILRI's trypanosomiasis research is to reduce poverty, improve food security and to conserve the environment, through sustainable improvements to controlling the disease. There are three broad themes: understanding the impact of trypanosomiasis within priority farming system and ecological contexts; development of improved diagnostic methods, and conducting research. The research findings contribute to the basic and applied science needed for improving trypanosomiasis control in animals and humans.

Research is being conducted in trypanotolerance, vaccine development, diagnostics and molecular biology, epidemiology, socio-economics, environmental monitoring and the development of decision-support tools.

Trypanotolerance has been a major research focus for more than two decades. Vaccine development was reviewed recently. Following the review, a series of trials to assess the infection-blocking vaccines targeting the flagellar pocket were conducted. The trials did not demonstrate efficacy, and development of the anti-infection vaccines was discontinued early in 2001. Work continues on vaccine as a joint project between CIRAD-EMVT, IRD and ILRI.

Epidemiological research focuses on assessment of alternative control options, on drug resistance, and on cattle-human transmission of rhodesiense sleeping sickness. New socio-economic research projects have begun to assess delivery systems, to estimate transaction costs and to assess the economic issues associated with tsetse and trypanosomiasis control. ILRI is also placing increasing importance on environmental

monitoring and impact assessment of changes in agricultural activity including disease control programmes.

ITC

Research work at the International Trypanotolerant Centre is organised according to low-input systems, market-oriented (intensive) systems, and those that cut across the two systems. All institutional projects are under the three programmes; low-input systems improvement programme (LISIP), Market-Oriented Systems Improvement Programme (MOSIP) and Systems Overlaps and Linkages Improvement Programme (SOLIP).

The mission of ITC is to contribute to the efforts of increasing livestock productivity and utilisation in the West Africa region through the optimal and sustainable exploitation of genetic resistance of indigenous breeds of livestock for the welfare of the human populations. The Centre closely collaborates with the various NARS in the region and has contributed towards strengthening their capacities. Also ITC collaborates closely with CIRDES and ILRI, with whom they have some joint projects.

Through scientific publications, ITC has demonstrated to the international research and development communities the worthiness of trypanotolerant livestock of West Africa.

OIE(NTTAT)

The Non-Tsetse Transmitted Animal Trypanosomiasis group (NTTAT) which originally sought to control *Trypanosoma evansi,* has had its activities extended to other trypanosome infections not transmitted by tsetse flies. Research workers are encouraged to carry out research in their respective countries. Aspects being looked at now include diagnostics and chemotherapy. The main research findings vary greatly and concern epidemiology, diagnostic methods and basic molecular biology techniques.

CIRDES

CIRDES was born from the CRTA (Centre de recherche sur la trypanosomose animale) in 1992, as a result of a decision by Heads of State of the five "Conseil de l'entente" Member States: Benin, Burkina Faso, Côte d'Ivoire, Niger and Togo. Its activities also extend to Mali and Ghana. Research and the fight against trypanosomiasis and its vectors largely dominate CIRDES activities. The activities related to trypanosomiasis are: disease diagnosis, chemoresistance, trypanotolerance, tsetse control, and the socio-economic impact of tsetse and trypanosomiasis control.

During the last two years, CIRDES has been restructured and its scientific activities primarily concern the implementation of the Joint Programme for Research/Development on Livestock (PROCORDEL). The research projects submitted by the NARS have been selected and are financed by PROCORDEL. Each project is based in the NARS under the responsibility of a national research worker. Training programmes are provided for the duration of the project, on diagnosis and the identification of epidemiologically important areas.

WHO

The World Health Organisation (WHO) reported considerable progress in the development of public-private sector partnerships that had resulted in securing supplies of essential drugs to treat sleeping sickness, for surveillance activities, and for development of new and improved drugs. WHO and the pharmaceutical company Aventis have an agreement under which $25 million was provided for drugs, surveillance, development of oral formulation, and other research and development activities. Countries requiring these drugs can request them from WHO and will only pay shipping costs. Although not directly involving WHO, a grant of $15.1 million has been obtained from the Gates Foundation for the development of new drugs for the treatment of HAT.

Despite the above progress, the need for advocacy for HAT for additional funds still continues as the Aventis Agreement is only for 5 years.

Country and regional programme reports

Sudan

Livestock in the Sudan accounts for more than 20% of GDP of foreign earnings, but 80% of the national herd is under trypanosomiasis challenge. About 20% of the human population is at risk of sleeping sickness, and the disease is ranked among the five top endemic diseases, especially in the southern parts of the country.

In the Sudan five government ministries and a number of universities and institutions are, in one way or other, involved in tsetse and trypanosomiasis management. A national strategy document for tsetse and trypanosomiasis control has been produced. Ongoing activities include mapping of the northern limits of tsetse, the role of small ruminants as reservoirs, drug resistance work, renovation and rehabilitation of the infrastructure, and maintenance of links with other groups in the region (EANETT), as well as with international organisations (FAO, WHO, IAEA) and NGOs (MSF, VSF, etc). Future plans include continuation of disease mapping in man and animals, and development of intervention strategies suited to the varied situations of the Sudan.

Nigeria

Tsetse flies infest over 80% of the Nigerian land mass. Increased human activities have altered tsetse distribution resulting in the disappearance of the fusca group from the southern Guinea savanna and collapse of some of the *G. morsitans* belts.

Animal trypanosomiasis threatens over 11 million head of cattle. An average trypanosomiasis infection rate in livestock during 1999-2001 was 10.9% in cattle, 1.9% in sheep and 4.5% in goats from various ecological zones. The disease in cattle is on the increase due to the menace of tsetse flies, drug resistance and presence of other haematophagous flies.

Human trypanosomiasis due to *Trypanosoma brucei gambiense* is currently ravaging parts of Delta State, south-western Nigeria. A disease surveillance of the area by NITR, in collaboration with WHO, revealed 10% sero-positive and 5.9% parasitologically positive cases from 4966 voluntary persons. Between 1999 and 2000, 27 confirmed cases were treated in one hospital at Eku.

Angola

Angola still experiences high numbers of sleeping sickness cases. However, there was a considerable drop of cases in the population examined between 1999 and 2001 from 5351 cases in 1999 to 1355 in 2001. Government efforts to control sleeping sickness are augmented by a number of local and international NGOs and church organisations. Treatment campaigns have yielded positive results as numbers of new cases keep reducing. However inaccessibility to patients due to the war situation in the country still presents a major obstacle to the provision of regular medical services.

Animal trypanosomiasis is equally widespread among the few livestock as most were decimated by war. There are plans to import more trypanotolerant cattle. The main constraints in the fight against tsetse and trypanosomiasis are: limited accessibility, insufficient human resources, lack of some equipment, and destruction of health infrastructure.

Uganda

The Government of Uganda recognises the tsetse and trypanosomiasis problem as a major hindrance to rural development. An assessment of the tsetse problem shows that trypanosomiasis is equally important in livestock and humans. Currently three on-going projects, namely FITCA, Primary Health Care Project and the Integrated SIT-Based Intervention Against Tsetse Flies in Buvuma Islands, are focussed on achieving manageable levels of tsetse and acceptable levels of sleeping sickness and animal trypanosomiasis.

The Regional Tsetse and Trypanosomiasis Control Programme for Southern Africa (RTTCP): The final balance

The original approach of RTTCP to eradicate tsetse flies from the SADC region was abandoned, in view of changing circumstances for local (national) tsetse and trypanosomiasis management schemes. In the formulation of national strategic plans, a pathway was defined which entailed firstly, the identification of priority areas using set criteria, and secondly, proposing appropriate control methods based on information generated by surveys and data analysis. Over a period of five years a critical mass of information was obtained that enabled the elaboration of a framework for strategy development.

RECOMMENDATIONS OF THE 26TH ISCTRC CONFERENCE

The Council recognises and commends:

The significant progress made since the 25th Conference by WHO, in partnership with the private sector, to secure significant resources for the control of sleeping sickness; and

The progress made in the last two years in founding PATTEC and securing the support of the OAU Heads of State for the goal of tsetse eradication

The ISCTRC council requests:

That the OAU member states incorporate the PATTEC Plan of Action into their national development plans;
That all participants of the 26th ISCTRC meeting return to their home countries and organisations and endeavour to secure support to facilitate implementation of the PATTEC Plan of Action; and
That the international community supports the implementation of PATTEC's Plan of Action.

JUDITH CHILD: AN APPRECIATION

As regular readers of *TTIQ* will already be aware, Judith Child has had to give up her editorship of the quarterly, for personal reasons. Her period as editor of *TTIQ* lasted for 19 years. Before that, she worked as a general scientific editor for the Centre for Overseas Pest Research (later the Natural Resources Institute).

When *TTIQ* was started in 1978, as a joint undertaking by FAO, WHO, COPR and OAU, COPR was made responsible for the day-to-day running of the project. The work of the editor involved, not only the compilation, production, printing and distribution of both English and French editions of the journal, but also responsibility for management of the funds provided by COPR and the other sponsoring organisations. Over the years, as costs rose and some of the original sponsors had to reduce their contributions, Judith sought additional funding from new sponsors to keep *TTIQ* going and championed its cause when its future was threatened by changes of policy within COPR/TDRI/NRI. She had to take early retirement in 1994, but continued working on *TTIQ* as a freelance on contract to NRI. In 1996, FAO assumed responsibility for management, printing and distribution, while keeping Judith on as editor.

In her years of service, Judith made various changes in the arrangement of the different sections of *TTIQ*, increasing the number of topics for which abstracts were provided and incorporating suggestions from the readership whenever possible. Many readers sent her copies of publications to include in *TTIQ* and some kept up a regular supply of reprints over a period of many years; some told her how useful they found *TTIQ* and were complimentary about its quality. Judith has remarked that she is most grateful for this feedback and appreciation.

Over the years that she worked as editor, Judith witnessed some changes in tsetse control, particularly a shift from aerial and ground spraying to community participation using traps which local people can make for themselves, and the development of odour attractants. Tsetse control is now also more integrated with changes in land use. There have been some useful developments in disease diagnosis but depressingly few new trypanocides. There have been many fresh initiatives which have promised much but which have so far failed to make a great deal of difference. Essentially the problem is lack of money in the affected countries and civil war disrupting disease surveillance and continuity of the remedial effort. Judith would like to offer her best wishes for the future to all concerned in the continuing fight against tsetse and trypanosomiasis.

Although Judith, like many laboratory-based researchers, has had little direct contact with tsetse and trypanosomiasis in the field, she has made a significant contribution to the fight against the disease and its vector. We wish her peace and happiness in her well-

earned retirement; she may be assured that her long years of editorial work have been appreciated by the tsetse-trypanosomiasis community.

Dr. Samuel Jutzi, Director of Animal Production and Health Division, FAO, Rome.

SECTION B - ABSTRACTS

1. GENERAL (INCLUDING LAND USE)

11933 **Burri, C., 2001.** Are there new approaches to roll back trypanosomiasis? *Tropical Medicine and International Health*, **6** (5): 327-329.

Burri: Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland. [christian.burri@unibas.ch]

This editorial overview introduces a number of papers in an issue of Tropical Medicine and International Health dealing with the current increased prevalence of human African trypanosomiasis. This resurgence at first elicited relatively little attention from the public, funding agencies, politicians and scientists. However, the 1999 ISCTRC conference reflected a new awareness of the disease, and the OAU Heads of States and Governments signed a declaration of intent, in 2000, to eradicate tsetse flies from the African continent. Recently, the continuous efforts of WHO and NGOs have led to better awareness of these matters, and new administrative structures have been set up such as PAAT and the WHO Sleeping Sickness Treatment and Drug Resistance Network. Additionally, WHO Tropical Diseases Research group has re-instated trypanosomiasis in its list of diseases to give it priority status. The Drugs Working Group of the WHO Network mentioned above has been able to persuade the pharmaceutical industry to continue the production of drugs in current use. The Bill and Melinda Gates Foundation has made a grant towards the development of a new, orally applicable first-stage drug for sleeping sickness, with more than a dozen academic and industrial partners working together under the auspices of the University of North Carolina. For various reasons, much of the laboratory work conducted on *Trypanosoma brucei* is basic in nature: applied research papers form only a small minority of the published output. The papers presented in this issue cover epidemiology, disease management and attempts to improve treatment, including drug reactions and drug resistance. Biological diversity of the trypanosome parasite is also examined. It is concluded that co-ordinated efforts by all sectors, including the political one, are needed to bring this disease under control.

11934 **McDermott, J.J. and Coleman, P.G., 2001.** Comparing apples and oranges - model-based assessment of different tsetse-transmitted trypanosomosis control strategies. *International Journal for Parasitology*, **31** (5-6): 603-609.

McDermott: International Livestock Research Institute (ILRI), P.O.Box 30709, Nairobi, Kenya. [j.mcdermott@cgiar.org]

The current control strategies for tsetse-transmitted trypanosomosis in cattle (trypanocidal drugs, tsetse control and trypanotolerant cattle) are briefly reviewed and their adoption rates in different geographic regions of sub-Saharan Africa are presented. The impact of these control strategies and the potential use of vaccines, should they be developed, on trypanosomosis transmission, were compared using a mathematical model. The relative trypanosomosis prevalence compared with no control was estimated across a range of control coverages (from none to complete control coverage) by varying the

change in specific model parameters influenced by individual control measures. Based on this comparison, the relative rankings of the effect of control strategies on reducing disease prevalence were: vector control, vaccination, and drug use, in that order. In this model, trypanotolerance was assumed to decrease disease prevalence, but not to influence transmission. Differences in the predicted impact of control measures on the transmission of human sleeping sickness are discussed. Finally, the role of transmission model outputs as inputs for economic models to guide investment decisions for trypanosomosis control is emphasised.

11935 **Schofield, C.J. and Maudlin, I., 2001.** Trypanosomiasis control. *International Journal for Parasitology*, **31** (5-6): 615-620.

Maudlin: Centre for Tropical Veterinary Medicine, University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG UK. [imaudlin@vet.ed.ac.uk]

In July 2000, Heads of State of the 36th Session of the Organisation for African Unity signed a potentially important declaration on African trypanosomiasis, urging member states "to act collectively to rise to the challenge of eliminating the problem through concerted efforts in mobilising the necessary human, financial and material resources required to render Africa tsetse-free within the shortest time possible". To many, such an ambitious dream is received with some scepticism, recalling the doubts that surrounded a similar declaration signed in Brasilia in 1991, which paved the way for the Southern Cone Initiative against American trypanosomiasis (Chagas disease). True, the two diseases are quite different, but the operational challenges are quite similar, and there are sufficient biological parallels to suggest that the Latin American experience in controlling Chagas disease may provide a useful model for the control of African trypanosomiasis.

2. TSETSE BIOLOGY

(a) REARING OF TSETSE FLIES

11936 **Mutika, G.N., Opiyo, E. and Robinson, A.S., 2001.** Assessing mating performance of male *Glossina pallidipes* (Diptera : Glossinidae) using a walk-in field cage. *Bulletin of Entomological Research*, **91** (4): 281-287.

Mutika: Entomology Unit, FAO/IAEA Agriculture and Biotechnology Laboratory, Agency's Laboratories, A-2444 Seibersdorf, Austria. [G.Mutika@iaea.org]

To monitor the quality of male tsetse for use in the sterile insect technique (SIT), a field cage test was developed and evaluated. Mating competitiveness was tested with male *Glossina pallidipes* that emerged from pupae stored for different periods at 15°C. Control males were from pupae stored at 23-24°C and emerged at 26.5°C. Each sample of test males was divided into two groups with one group being irradiated at 120 Gy; the other group was not irradiated. More than 70% of the maximum possible number of mating

pairs occurred in all tests. Males emerged from pupae kept at low temperature and then irradiated formed a greater proportion of mating pairs than the controls. Males emerged from pupae kept at 15°C generally started mating more quickly than the standard colony males although there was no significant difference. Insemination rates were above 99%. Pooled data indicated that mean spermathecal values for females mated with irradiated males were significantly lower than for control males. The duration of copulation varied significantly between treatment groups and was significantly longer for irradiated male flies; there was no correlation between duration of copulation and mean spermathecal value.

(b) TAXONOMY, ANATOMY, PHYSIOLOGY, BIOCHEMISTRY

[See also **24**: no. 11948]

11937 **Akman, L. and Aksoy, S., 2001.** A novel application of gene arrays: *Escherichia coli* array provides insight into the biology of the obligate endosymbiont of tsetse flies. *Proceedings of the National Academy of Sciences of the United States of America*, **98** (13): 7546-7551.

Aksoy: Department of Epidemiology and Public Health, Section of Vector Biology, Yale University School of Medicine, 60 College Street, New Haven, CT 06510, USA. [serap.aksoy@yale.edu]

Symbiotic associations with microorganisms are pivotal in many insects. Yet, the functional roles of obligate symbionts have been difficult to study because it has not been possible to cultivate these organisms *in vitro*. The medically important tsetse fly (*Glossina*) relies on its obligate endosymbiont, *Wigglesworthia glossinidia*, a member of the Enterobacteriaceae and closely related to *Escherichia coli*, for fertility and possibly nutrition. We show here that the intracellular *Wigglesworthia* has a reduced genome size smaller than 770 kb. In an attempt to understand the composition of its genome, we used the gene arrays developed for *E. coli*. We were able to identify 650 orthologous genes in *Wigglesworthia* corresponding to ≈85% of its genome. The arrays were also applied for expression analysis using *Wigglesworthia* cDNA and 61 gene products were detected, presumably coding for some of its most abundant products. Overall, genes involved in cell processes, DNA replication, transcription and translation were found largely retained in the small genome of *Wigglesworthia*. In addition, genes coding for transport: proteins, chaperones, biosynthesis of cofactors and some amino acids, were found to comprise a significant portion, suggesting an important role for these proteins in its symbiotic life. Based on its expression profile, we predict that *Wigglesworthia* may be a facultative anaerobic organism that utilizes ammonia as its major source of nitrogen. We present an application of *E. coli* gene arrays to obtain broad genome information for a closely related organism in the absence of complete genome sequence data.

11938 **Akman, L., Rio, R.V.M., Beard, C.B. and Aksoy, S., 2001.** Genome size determination and coding capacity of *Sodalis glossinidius*, an enteric symbiont of tsetse flies, as revealed by hybridization to *Escherichia coli* gene arrays. *Journal of Bacteriology*, **183** (15): 4517-4525.

Aksoy: Department of Epidemiology and Public Health, Section of Vector Biology, Yale University School of Medicine, 60 College Street, New Haven, CT 06510, USA. [serap.aksoy@yale.edu]

Recent molecular characterization of various microbial genomes has revealed differences in genome size and coding capacity between obligate symbionts and intracellular pathogens versus free-living organisms. Multiple symbiotic microorganisms have evolved with tsetse fly, the vector of African trypanosomes, over long evolutionary times. Although these symbionts are indispensable for tsetse fecundity, the biochemical and molecular basis of their functional significance is unknown. Here, we report on the genomic aspects of the secondary symbiont *Sodalis glossinidius*. The genome size of *Sodalis* is approximately 2 Mb. Its DNA is subject to extensive methylation and based on some of its conserved gene sequences has an A+T content of only 45%, compared to the typically AT-rich genomes of endosymbionts. *Sodalis* also harbors an extrachromosomal plasmid about 134 kb in size. We used a novel approach to gain insight into *Sodalis* genomic contents, i.e. hybridizing its DNA to macroarrays developed for *Escherichia coli*, a closely related enteric bacterium. In this analysis we detected 1,800 orthologous genes, corresponding to about 85% of the *Sodalis* genome. The *Sodalis* genome has apparently retained its genes for DNA replication, transcription, translation, transport, and the biosynthesis of amino acids, nucleic acids, vitamins, and cofactors. However, many genes involved in energy metabolism and carbon compound assimilation are apparently missing, which may indicate an adaptation to the energy sources available in the only nutrient of the tsetse host, blood. We present gene arrays as a rapid tool for comparative genomics in the absence of whole genome sequence to advance our understanding of closely related bacteria.

11939 **Krafsur, E.S., Endsley, M.A., Wohlford, D.L., Griffiths, N.T. and Allsopp, R., 2001.** Genetic differentiation of *Glossina morsitans centralis* populations. *Insect Molecular Biology*, **10** (4): 387-395.

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Variation at mitochondrial and microsatellite loci was used to study the breeding and dispersal structure of *Glossina morsitans centralis*, in six natural populations from Botswana, the Caprivi Strip (Namibia), Zambia, and in a laboratory culture derived from Singida, Tanzania. Only seven mitochondrial haplotypes were found. Mean diversity averaged over the six natural populations was 0.216 ± 0.085. The fixation index F_{ST} = 0.866 indicated a high degree of genetic differentiation among populations. Fifty-three alleles were detected among six microsatellite loci and six natural populations. Mean microsatellite diversity was 0.702 ± 0.091. Depending on the estimating model used, fixation indices varied from 0.15 to 0.225 confirming that *G. m. centralis* populations are strongly subdivided. For all F_{ST} estimates, positive correlations were detected between pair-wise genetic distance measures and geographical distances. The difference in fixation indices estimated from mitochondrial or nuclear loci was explained by the greater sensitivity of mitochondrial genomes to genetic drift. Population differentiation can be

explained by genetic drift and the subsequent recovery of extant populations from small, discontinuous populations. These data confirm genetically the collapse and retreat of *G. m. centralis* populations caused by the rinderpest epizootic of the late 19th and early 20th centuries.

(c) DISTRIBUTION, ECOLOGY, BEHAVIOUR, POPULATION STUDIES

11940 **de La Rocque, S., Augusseau, X., Guillobez, S., Michel, V., De Wispelaere, G., Bauer, R. and Cuisance, D., 2001.** The changing distribution of two riverine tsetse flies over 15 years in an increasingly cultivated area of Burkina Faso. *Bulletin of Entomological Research*, **91** (3): 157-166.

de La Rocque: CIRAD-EMVT, CIRDES, BP 454, 01 Bobo Dioulasso, Burkina Faso. [stephane.delarocque@cirad.fr]

Changes in the distribution of two riverine tsetse flies, *Glossina tachinoides* and *Glossina palpalis gambiensis* are described in an agropastoral area of Burkina Faso subject to increasing human population pressure and land use change. Two similar entomological surveys (one trap every 100 m, 120 km of river) were conducted in 1981 and 1996. Changes in tsetse distribution were compared to land use changes through high resolution remote sensing imagery (LANDSAT, SPOT). There was a close relationship between proximity of crops relative to riverine forest and the density of *Glossina*. Where fields encroached on riverine vegetation, tsetse populations declined. Where the geomorphological structure was not well suited to agricultural activity, riverine vegetation and tsetse fly populations were relatively unaffected, even with intense agricultural activity nearby. In contrast, increased human activity and higher cattle densities in the surrounding savannah areas were associated with increased tsetse numbers. The results demonstrated a wide diversity of tsetse distribution and habitat within a few kilometres in an agro-pastoral landscape in West Africa.

11941 **Gouteux, J.-P., Artzrouni, M. and Jarry, M., 2001.** A density-dependent model with reinvasion for estimating tsetse fly populations (Diptera: Glossinidae) through trapping. *Bulletin of Entomological Research*, **91** (3): 177-183.

Gouteux: Laboratory of Molecular Ecology, IBEAS, Université de Pau, UPPA, 64000 Pau, France [jean-paul.gouteux@wanadoo.fr]

A simple density-dependent reinvasion model is described and used to estimate tsetse fly populations on the basis of removal trapping experiments. The model was tested on *Glossina fuscipes fuscipes* in the Central African Republic and *G. palpalis palpalis* in the Republic of Congo (Brazzaville). The density-dependence is modelled by postulating that the inflow of flies each day is proportional to the deficit relative to the equilibrium population. Non-linear least square techniques were used to estimate the following parameters: the daily capture rate, the strength of the density-dependence, and the equilibrium fly population, at the beginning and at the end of the trapping experiment. The model ignores birth and death rates of flies and is applicable only when a rapid decrease in population occurs over a short period (between 10 and 20 days). Over longer

periods one could not ignore the natural growth of the populations as well as other more complex density-dependent mechanisms.

11942 **Odulaja, A., Baumgärtner, J., Mihok, S. and Abu-Zinid, I.M., 2001.** Spatial and temporal distribution of tsetse fly trap catches at Nguruman, southwest Kenya. *Bulletin of Entomological Research*, **91** (3): 213-220.

Odulaja: ICIPE, P.O.Box 30772, Nairobi, Kenya. [aodulaja@icipe.org]

Spatial and temporal dynamics of rapidly growing populations of tsetse flies at Nguruman, southwest Kenya, during 1993-1995, were investigated, following six years of intensive population suppression with traps over a *c*.100 km^2 area. The two tsetse species present were randomly distributed in the short rainy season, but were aggregated in the dry and long rainy seasons. Maximum temperature was the dominant weather factor associated with the degree of aggregation. Trends in catches at 20 fixed sites along an 18 km north-south axis were weakly correlated between locations, possibly representing population sub-structuring. In particular, trends in population change were poorly correlated between the area with a long history of trapping suppression in the south and the area with a more recent history of suppression in the north. On a micro-geographic scale, correlations among paired trap catches were clearly related to geographical proximity for *Glossina pallidipes* ($r^2 = 0.55$), whereas this relationship was quite weak for *Glossina longipennis* ($r^2 = 0.12$). Positive correlations among trap catches were significant for sites separated by less than *c*. 3.8 km (*G. pallidipes*) or 4.8 km (*G. longipennis*). These results suggest the existence of different population substructures in the two species on a relatively small geographic scale.

3. TSETSE CONTROL (INCLUDING ENVIRONMENTAL SIDE EFFECTS)

[See also **24**: nos. 11934, 11937, 11947, 11969, 11970, 11975]

11943 **Curtis, C.F. and Davies, A.R., 2001.** Present use of pesticides for vector and allergen control and future requirements. (Review.) *Medical and Veterinary Entomology*, **15** (3): 231-235.

Curtis: Department of Infective and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. [chris.curtis@lshtm.ac.uk]

11944 **Dyck, V.A., Pan, H., Kassim S.S., Suleiman F.W., Mussa W.A., Saleh, K.M., Juma, K.G., Mkonyi, P.A., Holland W.G., van der Eerden, B.J.M. and Dwinger R.H., 2000.** Monitoring the incidence of trypanosomiasis in cattle during the release of sterilized tsetse flies on Unguja Island, Zanzibar. *Revue d'Elevage et de Médecine vétérinaire des Pays tropicaux,* **53** (3): 239-243.

Dyck: Department of Technical Cooperation, International Atomic Energy Agency, A-1400 Vienna, Austria. [ADyck@compuserve.com]

The incidence of trypanosomosis in sentinel cattle on Unguja Island, Zanzibar, was monitored every two to five months in 1994-97 to observe changes in disease transmission attributable logically to the application of insecticides, the release of sterilized tsetse flies (*Glossina austeni*) and the consequent decline and eradication of the wild tsetse population. Two parasitological techniques (microhaematocrit centrifuge and buffy coat) were used to monitor the disease incidence caused by *Trypanosoma congolense* and *T. vivax*. *Trypanosoma congolense* and *T. vivax* were detected in 1994 and 1995, but only *T. vivax* was detected thereafter. By 1997, the incidence of bovine trypanosomiasis was only 0.1%. There was evidently no increase in disease incidence due to the release of sterilized isometamidium chloride-treated male tsetse flies.

11945 **Hursey, B.S., 2001.** Sterile insect release and trypanosomiasis control: a plea for realism – Reply. (Letter.) *Trends in Parasitology*, **17** (9): 414.

Hursey: 1 Siding Terrace, Neath SA10 6RE, UK.

11946 **Molyneux, D.H., 2001.** Sterile insect release and trypanosomiasis control: a plea for realism. (Letter.) *Trends in Parasitology*, **17** (9): 413-414.

Molyneux: Lymphatic Filariasis Support Centre, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. [fahy@liverpool.ac.uk]

4. EPIDEMIOLOGY: VECTOR-HOST AND VECTOR PARASITE INTERACTIONS

11947 **Artzrouni M. and Gouteux J.-P., 2001.** A model of Gambian sleeping sickness with open vector populations. *IMI Journal of Mathematics Applied in Medicine and Biology*, **18**: 99-117.

Artzrouni: Department of Applied Mathematics, University of Pau, 64000 Pau, France. [marc.artzrouni@univ-pau.fr]

A compartmental model of Gambian sleeping sickness is described that takes into account density-dependent migratory flows of infected flies. Equilibrium and stability theorems are given which show that with a basic reproduction number R_0 below unity, then in the absence of reinvasion the disease goes to extinction. However, even a low prevalence rate among reinvading flies can then bring about significant equilibrium prevalence rates among humans. For a set of realistic parameter values we show that even in the case of a virulent parasite that keeps infected individuals in the first stage for as little as 4 to 8 months (durations for which there would be extinction with no infected reinvading flies) there is a prevalence rate in the range 13.0-36.9%, depending on whether 1 or 2% of reinvading flies are infected. A rate of convergence of the population dynamics is introduced and is interpreted in terms of a halving time of the infected population. It is argued that the persistence and/or extension of Gambian sleeping

sickness foci could be due either to a continuous reinvasion of infected flies or to slow dynamics.

11948 **Dale, C. and Welburn, S.C., 2001.** The endosymbionts of tsetse flies: manipulating host-parasite interactions. *International Journal for Parasitology*, **31** (5-6): 628-631.

Dale: Alexander Robertson Centre for Tropical Veterinary Medicine, Easter Bush, Roslin, Midlothian EH25 9RG UK. [cdale@ed.ac.uk]

Through understanding the mechanisms by which tsetse endosymbionts potentiate trypanosome susceptibility in tsetse, it may be possible to engineer modified endosymbionts which, when introduced into tsetse, render these insects incapable of transmitting parasites. In this study the effect of three different antibiotics on the endosymbiotic microflora of tsetse (*Glossina morsitans morsitans*) have been assayed. It is shown that the broad-spectrum antibiotics, ampicillin and tetracycline, have a dramatic impact on tsetse fecundity and pupal emergence, effectively rendering these insects sterile. This results from the loss of the tsetse primary endosymbiont, *Wigglesworthia glossinidia*, which is eradicated by ampicillin and tetracycline treatment. Using the sugar analogue and antibiotic, streptozotocin, specific elimination of the tsetse secondary endosymbiont, *Sodalis glossinidius*, with no observed detrimental effect upon *W. glossinidia,* is demonstrated. The specific eradication of *S. glossinidius* had a negligible effect upon the reproductive capability of tsetse but did effect a significant reduction in fly longevity. Furthermore, elimination of *S. glossinidius* resulted in increased refractoriness to trypanosome infection in tsetse, providing further evidence that *S. glossinidius* plays an important role in potentiating trypanosome susceptibility in this important disease vector. In the light of these findings, progress made towards developing recombinant *Sodalis* strains engineered to avoid potentiating trypanosome susceptibility in tsetse is highlighted. In particular, attention is focussed upon the chitinase/N-acetyl-D-glucosamine catabolic machinery of *Sodalis*, which has previously been implicated in causing immune inhibition in tsetse.

11949 **Hide, G. and Tilley, A., 2001.** Use of mobile genetic elements as tools for molecular epidemiology. [*T. brucei rhodesiense.*] *International Journal for Parasitology*, **31** (5-6): 599-602.

Hide: Centre for Molecular Epidemiology and Ecology, Division of Biological Sciences, University of Salford, Salford, M5 4WT UK.

Trypanosomiasis is a complex zoonotic disease where human-infective and non-human-infective strains of *Trypanosoma brucei* interact in the same transmission cycles. Differentiating these strains is paramount to understanding disease epidemiology. Restriction fragment length polymorphism analysis of repetitive DNA has provided such a method for distinguishing human and non-human isolates. Unfortunately, this approach requires large amounts of material and a more rapid approach is required. We have developed a novel technique, mobile genetic element-PCR, for assaying for positional variation of the mobile genetic element, RIME. The trypanosome genome contains up to

400 copies of RIME. Using this approach we have observed considerable variation between strains of *T. brucei*. Such a technique may offer potential as a method for differentiating non-human- and human-infective trypanosomes and shows promise as a rapid sensitive tool for investigating the epidemiology of sleeping sickness.

11950 **Molineaux, L. and Dietz, K., 1999.** Review of intra-host models of malaria. *Parassitologia*, **41** (1-3): 221-231.

Dietz: Institut für Medizinische Biometrie, Universität Tübingen, Westbahnhofstrasse 55, D-72070 Tübingen, Germany. [klaus.dietz@uni-tuebingen.de]

Intra-host models of malaria (and some related models of trypanosomiasis) are reviewed. A first section gives a short description of the different models, their purposes and the authors' conclusions. A second section discusses some common issues, including intra-host populations, the intra-host basic reproduction number (R_0) and growth rates, density regulation mechanisms (including acquired immunity), and the model's behaviour compared to that of *Plasmodium falciparum* in man.

11951 **Pays, E., Lips, S., Nolan, D., Vanhamme, L. and Pérez-Morga, D. 2001.** The VSG expression sites of *Trypanosoma brucei*: multipurpose tools for the adaptation of the parasite to mammalian hosts. (Review.) *Molecular and Biochemical Parasitology*, **114** (1): 1-16.

Pays: Laboratory of Molecular Parasitology, IBMM, Department of Molecular Biology, Free University of Brussels, 12, rue des Professeurs Jeener et Brachet, 8-6041 Gosselies, Belgium. [epays@dbm.ulb.ac.be]

The variant surface glycoprotein (VSG) genes of *Trypanosoma brucei* are transcribed in telomeric loci termed *VSG* expression sites (ESs). Despite permanent initiation of transcription in most if not all of these multiple loci, RNA elongation is abortive except in bloodstream forms where full transcription up to the *VSG* occurs only in a single ES at a time. The ESs active in bloodstream forms are polycistronic and contain several genes in addition to the *VSG*, named ES-associated genes (*ESAG*s). So far 12 *ESAG*s have been identified, some of which are present only in some ESs. Most of these genes encode surface proteins and this list includes different glycosyl phosphatidyl inositol (GPI)-anchored proteins such as the heterodimeric receptor for the host transferrin (*ESAG*7/6), integral membrane proteins such as the receptor-like transmembrane adenylyl cyclase (*ESAG*4) and a surface transporter (*ESAG*10). An interesting exception is *ESAG*8, which may encode a cell cycle regulator involved in the differentiation of long slender into short stumpy bloodstream forms. Several *ESAG*s belong to multigene families including pseudogenes and members transcribed out of the ESs, named genes related to *ESAG*s (*GRESAG*s). However, some *ESAG*s (7, 6 and 8) appear to be restricted to the ESs. Most of these genes can be deleted from the active ES without apparently affecting the phenotype of bloodstream form trypanosomes, probably either due to the expression of *ESAG*s from 'inactive' ESs (*ESAG*7/6) or due to the expression of *GRESAG*s (in particular, s4 and *GRESAG*s1). At least three *ESAG*s (*ESAG*7, *ESAG*6 and *SRA*) share the

evolutionary origin of *VSG*s. The presence of these latter genes in ESs may confer an increased capacity of the parasite for adaptation to various mammalian hosts, as suggested in the case of *ESAG*7/6 and proven for *SRA*, which allows *T. brucei* to infect humans. Similarly, the existence of a collection of slightly different *ESAG*4s in the multiple ESs might provide the parasite with adenylyl cyclase isoforms that may regulate growth in response to different environmental conditions. The high transcription rate and high recombination level that prevail in *VSG* ESs may have favored the generation and/or recruitment in these sites of genes whose hyper-evolution allows adaptation to a larger variety of hosts.

11952 **Pearson, T.W., 2001.** Procyclins, proteases and proteomics: dissecting trypanosomes in the tsetse fly. (Review.) *Trends in Microbiology*, **9** (7): 299-301.

Pearson: Department of Biochemistry and Microbiology, Petch Building, STN CSC, P.O.Box 3055, University of Victoria, Victoria, British Columbia V8W 3P6, Canada. [parasite@uvvm.uvic.ca]

The forms of African trypanosomes that live in tsetse fly vectors are coated with lipid-anchored proteins and glycoproteins known collectively as procyclins. Procyclins are expressed during development in the fly in a multiplicity of isoforms yet their functions remain unknown. Recent studies involving a multidisciplinary synthesis of tsetse biology, immunochemistry, biological chemistry and mass spectrometry have yielded much new information about procyclins, which could now provide an unparalleled view of the dynamic molecular interactions between this parasite and its insect vector.

11953 **Pépin, J. and Méda, H.A., 2001.** The epidemiology and control of human African trypanosomiasis. *Advances in Parasitology,* **49**: 71-132.

Pépin: Infectious Diseases Division, Centre for International Health, University of Sherbrooke 3001, 12th Avenue North, Sherbrooke, Québec, J1H 5N4 Canada.

The review covers: historical background, current disease burden, measures of incidence and prevalence, geographical distribution, epidemiological principles of gambian trypanosomiasis, epidemiology of rhodesian trypanosomiasis, and control of African trypanosomiasis: principles, methods and strategies.

11954 **Seed, J.R., 2001.** African trypanosomiasis research: 100 years of progress, but questions and problems still remain. [*T. brucei.*] *International Journal for Parasitology*, **31** (5-6): 434-442.

Seed: Department of Epidemiology, School of Public Health, University of North Carolina, CB 7400, McGavran-Greenberg Hall, Chapel, NC 27599-7400, USA. [rseed@sph.unc.edu]

Past and present progress in our understanding of African trypanosomiasis is briefly reviewed. Although tremendous scientific strides have been achieved, an epidemic of the disease is currently underway. Three areas of research, which are believed necessary for the control of African trypanosomiasis, are discussed. It is suggested that a better understanding of the host-parasite relationship is essential; more emphasis and a broader approach to drug development is required; and finally, further research into the socio-economic aspects of African trypanosomiasis is urgently needed before the human disease can again be controlled.

5. HUMAN TRYPANOSOMIASIS

(a) SURVEILLANCE

11955 **Cattand, P., Jannin, J. and Lucas, P., 2001.** Sleeping sickness surveillance: an essential step towards elimination. *Tropical Medicine and International Health*, **6** (5): 348-361.

Cattand: Association against Trypanosomiasis in Africa, 1 rue de l'Hotel Dieu, 74200 Thonon, France.

In the last decades, with little or no surveillance, sleeping sickness has returned to alarming levels comparable to the early twentieth century. Sixty million people are considered at risk but only 3-4 million are under surveillance, yielding some 45,000 new cases annually. It is estimated that at least 300,000-500,000 people are presently infected. Despite the almost universal presence of the vector in sub-Saharan Africa and the existence of an animal parasite reservoir, it is technically feasible to control and eliminate the disease as a public health problem. The authors describe, step-by-step, a surveillance method based on the epidemiological status of the village and using several approaches ranging from passive to active surveillance. Co-ordinated by the WHO, such surveillance has been started in several countries. Epidemiological data is spatially linked to the village, geographical co-ordinates of which are collected using a Global Positioning System (GPS). Information is transmitted to WHO through the internet. Data analysis and mapping are carried out using GIS software and thematic maps are generated to illustrate epidemiological status. Examples from Central African Republic (CAR), Cameroon and Gabon are given to illustrate the process and the mapping.

11956 **Fèvre, E.M., Coleman, P.G., Odiit, M., Magona, J.W., Welburn, S.C. and Woolhouse, M.E.J., 2001.** The origins of a new *Trypanosoma brucei rhodesiense* sleeping sickness outbreak in eastern Uganda. *Lancet*, **358** (9282): 625-628.

Fèvre: Centre for Tropical Veterinary Medicine, University of Edinburgh, Easter Bush, Roslin, Midlothian EH25 9RG, UK. [Eric.Fevre@ed.ac.uk]

Sleeping sickness, caused by two trypanosome subspecies, *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, is a parasitic disease transmitted by the tsetse fly in sub-

Saharan Africa. We report on a recent outbreak of *T. b. rhodesiense* sleeping sickness outside the established south-east Ugandan focus, in Soroti District where the disease had previously been absent. Soroti District has been the subject of large-scale livestock restocking activities and, because domestic cattle are important reservoirs of *T. b. rhodesiense*, we investigated the role of cattle in the origins of the outbreak. We identified the origins of cattle entering the outbreak area in the four years preceding the outbreak. A matched case-control study was conducted to assess whether the distance of villages from the main market involved with restocking was a risk factor for sleeping sickness. We investigated the spatial clustering of sleeping sickness cases at the start of the outbreak. Over 50% (1510 of 2796) of cattle traded at the market were reported to have originated from endemic sleeping sickness areas. The case-control study revealed that distance to the cattle market was a highly significant risk factor for sleeping sickness ($p<0.001$) and that there was a significant clustering of cases (27 of 28) close to the market at the start of the outbreak ($p<0.001$). As the outbreak progressed, the average distance of cases moved away from the cattle market (0.014 km per day, 95% CI 0.008-0.020 km per day, $p<0.001$). The results are consistent with the disease being introduced by cattle infected with *T. b. rhodesiense* imported to the market from the endemic sleeping sickness focus. The subsequent spread of the disease away from the market suggests that sleeping sickness is becoming established in this new focus. Public health measures directed at controlling the infection in the animal reservoir should be considered to prevent the spread of sleeping sickness.

11957 **Moore, A. and Richer M., 2001.** Re-emergence of epidemic sleeping sickness in southern Sudan. *Tropical Medicine and International Health*, **6** (5): 342-347.

Moore: Division of Parasitic Diseases, M/S F-22, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341, USA. [ary2@cdc.gov]

A resurgence of sleeping sickness developed in southern Sudan during the past decade. Prevalence of confirmed *Trypanosoma brucei gambiense* infection in humans now exceeds 5% in several foci. From 1997 to 1999, trypanosomiasis control programmes in three counties of Western Equatoria Province detected 3,785 new cases among 67,181 persons screened. A major contributing factor in the re-emergence of epidemic sleeping sickness was the lack of active case-finding throughout the 1990s. Although the situation is improving in sites where trypanosomiasis control programmes have been recently implemented, co-ordination and additional international assistance are needed to bring sleeping sickness under control in Sudan.

11958 **Seed, J.R. and Black, S.J., 2001.** The classic paper of Tobie, Von Brand, and Mehlman (1950) revisited. (Editorial note.) *Journal of Parasitology*, **87** (4): 718-720.

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11959 **Stanghellini A. and Josenando T., 2001.** The situation of sleeping sickness in Angola: a calamity. *Tropical Medicine and International Health,* **6** (5): 330-334.

Stanghellini: 4 Le Bourg Nord, 33660 Puynormand, France.

Although nearly one-fifth of the Angolan population is at risk of becoming infected with trypanosomiasis, only 6% currently have access to surveillance and treatment because of the war and its resultant destruction of the country's infrastructure. The paper outlines the history of human African trypanosomiasis control activities in Angola and reviews what measures need to be taken to re-establish them.

11960 **Van Nieuwenhove, S., Betu-Ku-Mesu, V.K., Diabakana, P.M., Declercq, L. and Bilenge, C.M.M., 2001.** Sleeping sickness resurgence in the DRC: the past decade. *Tropical Medicine and International Health*, **6** (5): 335-341.

Bilenge: Bureau Central de la Trypanosomiase, Kinshasa, DCR. [bctrdc@ic.cd]

An overview of the evolution of sleeping sickness and control activities in the DRC during the period 1989-1998 is presented. A resurgence was already developing in the mid-1980s and, after a breakdown of active case-finding between 1990 and 1993, annual detection rates attained levels similar to those of the late 1920s. Although a staggering number of 150 591 new cases have been detected during the past decade, the problem is ignored by most of the international community. The major cause for the resurgence appears to be the interruption of active case-finding for a prolonged period of time. Control activities have improved considerably in recent years, but a lot remains to be done and supplementary resources are needed.

(b) PATHOLOGY AND IMMUNOLOGY

[See also **24**: nos. 11963, 11999]

(c) TREATMENT

[See also **24**: nos. 11954, 12000, 12043]

11961 **Anon., 2001.** Drug company wakes up to sleeping sickness needs. (News item.) *International Journal of Epidemiology*, **30** (4): 918.

It is reported that Aventis pharmaceuticals has agreed to make the drug eflornithine, used to treat sleeping sickness, available free to African countries where the parasitic disease is endemic. In addition, it is reported that the company has promised US$25 million to support WHO's sleeping sickness treatment and research programmes.

11962 **Barrett, M.P., 2001.** Veterinary link to drug resistance in human African trypanosomiasis? *Lancet*, **358** (9282): 603-604.

Barrett: Division of Infection and Immunity, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow G12 8QQ, Lanarkshire, UK.

This paper raises the question whether resistance to the drugs used to combat HAT might arise in trypanosomes infecting drug-treated cattle.

11963 **Blum, J., Nkunku, S. and Burri, C., 2001.** Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. *Tropical Medicine and International Health*, **6** (5): 390-400.

Blum: Swiss Tropical Institute, Socinstr. 57, 4002 Basel, Switzerland. [blum@keep.touch.ch]

Encephalopathies are the most feared complications of sleeping sickness treatment with melarsoprol. To investigate the existence of risk factors, the incidence of encephalopathic syndromes and the relationship between the development of different types of encephalopathies and the clinical outcome were studied in a clinical trial with 588 patients under treatment with melarsoprol. The thirty eight encephalopathy cases were classified into three types according to the leading clinical picture: coma type, convulsion type and psychotic reactions. Nine patients were attributed to the convulsion type, defined as a transient event of short duration with convulsions followed by a post-ictal phase, without signs of a generalized disease. None of these patients died from the reaction. Febrile reactions in the 48 h preceding the reaction were generally not observed in this group. Twenty-five patients were attributed to the coma type, which is a progredient coma lasting several days. Those patients often had signs of a generalized disease such as fever (84%), headache (72%) or bullous skin (8%) reactions. The risk of mortality was high in this group (52%). About 14/16 patients with encephalopathic syndrome of the coma type were infected with malaria. Patients with psychotic reactions or abnormal psychiatric behaviour (3/38) and one patient who died after alcohol intake were excluded from the analysis. The overall rate of encephalopathic syndromes in the cases analysed (n = 34) was 5.8%, of which 38.2% died. We did not find any parameters of predictive value for the risk of developing an encephalopathic syndrome based on the symptoms and signs before treatment initiation. The appearance during treatment of febrile reactions (RR 11.5), headache (RR 2.5), bullous eruptions (RR 4.5) and systolic hypotension (RR 2.6) w associated with an increased risk for the occurrence of encephalopathic syndromes especially of the coma type.

11964 **Burri, C. and Keiser, J., 2001.** Pharmacokinetic investigations in patients from northern Angola refractory to melarsoprol treatment. *Tropical Medicine and International Health*, **6** (5): 412-420.

Burri: Swiss Tropical Institute, PO Box, CH-4002 Basel, Switzerland. [christian.burri@unibas.ch]

Melarsoprol, an organo-arsenical drug, has been the drug of choice for late-stage trypanosomiasis for 50 years. Because of the lack of alternatives any abatement of this medication will have a dramatic negative impact on the perspectives for patients. As a large number of patients refractory to melarsoprol treatment was recently reported from northern Uganda and northern Angola, we investigated in northern Angola whether interpatient pharmacokinetic differences influence the outcome of melarsoprol treatment. Drug levels were determined by a biological assay in serum and cerebrospinal fluid (CSF) of 22 patients. Nine patients could be successfully treated, eight were refractory and the outcome was unclear or no adequate follow-up information was available for five patients. No differences in the pharmacokinetic parameters (maximum serum concentration C_{max}, half-life $t_{½\beta}$, total clearance C_L and the volume of distribution V_{ss}) could be detected between the groups. Serum and CSF concentrations for all patients were in the expected range. This result indicates that other underlying factors are responsible for treatment failures.

11965 **Matovu, E., Enyaru, J.C.K., Legros, D., Schmid, C., Seebeck, T. and Kaminsky, R., 2001.** Melarsoprol refractory *T-b. gambiense* from Omugo, north-western Uganda. *Tropical Medicine and International Health*, **6** (5): 407-411.

Kaminsky: Novartis Centre de recherche santé animale SA, 1566 St-Aubin, Switzerland. [ronald.kaminsky@ah.novartis.com]

Culture adapted *Trypanosoma brucei gambiense* isolated from Northwest Uganda were exposed to 0.001-0.14 µg/ml melarsoprol or 1.56-100 µg/ml DL-α-difluoromethylornithine (DFMO). Minimum inhibitory concentrations (MICs) of each drug were scored for each isolate after a period of 10 days drug exposure. The results indicate that *T. b. gambiense* isolates from Northwest Uganda had elevated MIC values for melarsoprol ranging from 0.009 to 0.072 µg/ml as compared with *T. b. gambiense* isolates from Côte d'Ivoire with MIC values ranging from 0.001 to 0.018 µg/ml or with *T. b. rhodesiense* from Southeast Uganda with MIC values from 0.001 to 0.009 µg/ml. All MIC values obtained fell below expected peak melarsoprol concentrations in serum of treated patients. However, it may not be possible to maintain constant drug concentrations in serum of patients as was the case in our *in vitro* experiments. Importantly, the MIC of 0.072 µg/ml exhibited by one of the isolates from Northwest Uganda was above levels attainable in CSF indicating that this isolate would probably not be eliminated from CSF of treated patients. PCR amplification of the gene encoding the P2-like adenosine transporter followed by restriction digestion with *Sfa* NI enzyme revealed presence of fragments previously observed in a trypanosome clone with laboratory-induced arsenic resistance. From our findings it appears that reduced drug susceptibility may be one factor for the frequent relapses of sleeping sickness after melarsoprol treatment occurring in Northwest Uganda.

11966 **Matovu, E., Seebeck, T., Enyaru, J.C.K. and Kaminsky, R., 2001.** Drug resistance in *Trypanosoma brucei* spp., the causative agents of sleeping sickness in man and nagana in cattle. (Review.) *Microbes and Infection*, **3** (9): 763-770.

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Drug resistance in pathogenic trypanosomes threatens successful control of fatal sleeping sickness in man and hinders economic livestock production in sub-Saharan Africa. We report on the occurrence and development of drug resistance, and discuss the genetic basis of such resistance in *Trypanosoma brucei*. Understanding these mechanisms at the molecular level will enable improved management of existing drugs and provide valuable clues to the development of new trypanocides.

6. ANIMAL TRYPANOSOMIASIS

(a) SURVEY AND DISTRIBUTION

[See also **24**: no. 11944]

11967 **Desquesnes, M., McLaughlin, G., Zoungrana, A. and Dávila, A.M.R., 2001.** Detection and identification of *Trypanosoma* of African livestock through a single PCR based on internal transcribed spacer 1 of rDNA. [*T. brucei*.] *International Journal for Parasitology*, **31** (5-6): 610-614.

Desquesnes: CIRAD-EMVT BP 5035, 34032 Montpellier, France. [marc.desquesnes@cirad.fr]

Primers hybridising with the rDNA cistron have previously been evaluated for PCR diagnosis specific for kinetoplastids, and shown to detect and differentiate the *Trypanosoma brucei* complex and *T. cruzi*. Kin1 and Kin2 primers, amplifying internal transcribed spacer 1, were subsequently evaluated for the diagnosis of African livestock trypanosomosis. Based on the size of the PCR products obtained, Kin primers allowed detection and identification of three *T. congolense* types (savannah, forest and Kenya Coast), with distinction among themselves and from the subgenus *Trypanozoon* (*T. brucei* spp., *Trypanosoma evansi* and *T. equiperdum*), *Trypanosoma vivax*, *Trypanosoma simiae* and *Trypanosoma theileri*. These primers were shown to be suitable for the sensitive and type-specific diagnosis of African livestock trypanosome isolates through a single PCR even in the case of multi-taxa samples. With field samples (buffy coat from cattle blood) sensitivity was close to the sensitivity observed in single reactions with the classical specific primers for the *Trypanozoon* subgenus and *T. congolense*-type savannah, but was lower for detection of *T. vivax*. Additional reaction, improvement of DNA preparation, and/or new primers design are necessary to improve the sensitivity for detection of *T. vivax* in field samples. However, these primers are suitable for isolate typing through a single PCR.

11968 **Gibson, W.C., Stevens, J.R., Mwendia, C.M.T., Makumi, J.N., Ngotho, J.M. and Ndung'u, J.M., 2001.** Unravelling the phylogenetic relationships of African trypanosomes of suids. *Parasitology*, **122** (6): 625-631.

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African trypanosomes of the subgenera *Nannomonas* and *Pycnomonas* have been recorded from both wild and domestic suids. However, complete descriptions of some of these trypanosomes with regard to host range, pathogenicity, transmission and distribution are still lacking. Neither the recently described *Trypanosoma* (*Nannomonas*) *godfrei* nor *Trypanosoma* (*Nannomonas*) *congolense* Tsavo have been isolated from mammalian hosts, while *Trypanosoma* (*Pycnomonas*) *suis* remains the rarest of the Salivarian trypanosomes. The only isolate presumed to be of the latter species is maintained at KETRI, Nairobi. We present here the results of characterization of this isolate by morphology, tsetse transmission, the use of species-specific DNA probes and DNA sequence analysis. Morphology in stained blood smears revealed a small trypanosome with a free flagellum. Experimental transmission through *Glossina morsitans morsitans* showed a developmental cycle typical of subgenus *Nannomonas*. A positive identification was obtained with species-specific PCR primers for *T. congolense* Tsavo; moreover, the sequence of the SSU rRNA gene was almost identical to that of *T. congolense* Tsavo on database. In phylogenetic analysis of the SSU rRNA genes of Salivarian trypanosomes, *T. congolense* Tsavo grouped with *T. simiae* rather than *T. congolense*, suggesting that the name *T. simiae* Tsavo is more appropriate.

11969 **Van den Bossche, P., 2001.** Some general aspects of the distribution and epidemiology of bovine trypanosomosis in southern Africa. *International Journal for Parasitology*, **31** (5-6): 592-598.

Van den Bossche: Institute of Tropical Medicine, Veterinary Department, Nationalestraat 155, 2000 Antwerpen, Belgium. [pvdbossche@itg.be]

Bovine trypanosomosis occurs in vast areas of southern Africa. Its epidemiology and impact on cattle production are determined largely by the level of interaction between tsetse and cattle. Four situations can be distinguished. First, areas where cattle are absent. Second, zones where cattle have been introduced in game areas but where game is still abundant and constitutes the major source of food for tsetse. Third, areas where, often because of human interference, the density of game animals is low and cattle constitute the main source of food, and finally, areas where cattle occur at the edge of tsetse-infested zones. In southern Africa, the impact of the disease on cattle production varies according to the epidemiological circumstances. The disease has an epidemic character with significant impacts on production in areas where cattle have been introduced recently or along the interface between tsetse-infested game areas and tsetse-free cultivated areas. Bovine trypanosomosis has an endemic character, with little impact on production, in areas where tsetse mainly feed on cattle and where the invasion of tsetse is low. Options for the control of bovine trypanosomosis will vary according to the epidemiological circumstances. In particular, the control of tsetse with insecticide-treated cattle will only be effective when a large proportion of feeds are taken from cattle over a large area and when the invasion of tsetse can be reduced sufficiently.

11970 **Van den Bossche, P., Shumba, W., Njagu, C. and Shereni, W., 2001.** The distribution of bovine trypanosomosis in Zimbabwe and an evaluation of the value of an anti-trypanosomal antibody detection ELISA as a tool for monitoring the effectiveness of tsetse control operations. *Tropical Animal Health and Production*, **33** (5): 391-405.

Van den Bossche: Institute of Tropical Medicine, Veterinary Department, Nationalestraat 155, 2000 Antwerp, Belgium. [pvdbossche@itg.be]

Tsetse flies have been cleared from large areas of Zimbabwe during the past 65 years. In most areas, they are prevented from re-invading cleared areas by barriers of odour-baited, insecticide-treated targets. A trypanosomosis survey was conducted to determine the effectiveness of such barriers against re-invasion and to confirm the absence of tsetse in areas where they had previously been eradicated. Parasitological diagnostic methods and an anti-trypanosomal antibody detection enzyme-linked immunosorbent assay (antibody ELISA) were used. The prevalence of trypanosomal infections in the tsetse-cleared areas was generally low. However, the prevalence of anti-trypanosomal antibodies was unexpectedly high in some areas. This high proportion of cattle with antibodies could, in most cases, be explained by recent or historic information on the distribution and density of tsetse. The results from the survey demonstrated the value of anti-trypanosomal antibody detection as an additional sensitive tool for monitoring the effectiveness of tsetse control operations.

(b) PATHOLOGY AND IMMUNOLOGY

[See also **24**: no. 11999]

11971 **Black, S.J., Sicard, E.L., Murphy, N. and Nolan, D., 2001.** Innate and acquired control of trypanosome parasitaemia in Cape buffalo. *International Journal for Parasitology*, **31** (5-6): 562-565.

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The review discusses the roles of serum xanthine oxidase, serum catalase and trypanosome-specific immune responses in the regulation of the level of trypanosome parasitaemic waves in Cape buffalo.

11972 **Greiner, M., Mattioli, R.C., Faye, J., Rebeski, D., Winger, E. and Mehlitz, D., 2001.** A survival analysis of trypanosomosis diagnostic-test performance under natural infection challenge. *Preventive Veterinary Medicine*, **51** (1-2): 51-62.

Greiner: Department of International Animal Health, Institut für Parasitologie und Tropenveterinarmedizin, Freie Universität Berlin, Königsweg 67, 14163 Berlin, Germany. [mgreiner@vetmed.fu-berlin.de]

Little is known about the time-to-first detection and the time difference (TD) between first parasitological and first serological diagnosis of *Trypanosoma* spp. infections under natural infection challenge in cattle. The objective of our study was to estimate these measures of "longitudinal aspects" of diagnostic performance and to investigate potential biological factors. Emphasis was on diagnosis at the genus level (*Trypanosoma* spp.). Twelve N'Dama, 12 Gobra zebu and 12 N'Dama × Gobra (F_1) crossbred cattle (all animals non-infected at the start of the experiment, six male and six female animals in each cohort) were exposed to natural high tsetse challenge in the Niamina East area in The Gambia. The animals were investigated parasitologically (detection of trypanosomes by buffy-coat technique), serologically (detection of *T. brucei*, *T. congolense* and *T. vivax* antigen by enzyme-linked immunosorbent assay (ELISA)) and clinically (packed-cell volume, PCV) over a period of 180 days. The time-to-first detection of trypanosomes, trypanosomal antigen (cut-off as suggested by test supplier) and drop in PCV (subject-based cut-off values) were recorded as outcomes of interest. Thus, incidence was assessed parasitologically (I_p), serologically (I_s) and clinically (I_c). Recurrent events were not considered. The TD between first parasitological and first serological detection was established as I_s time minus I_p time. The effect of breed and sex on the time-to-first detection and on TD was investigated using Cox (proportional hazard) regression and ANOVA, respectively. We found that time-to-first parasitological detection of trypanosomosis in N'Dama animals was significantly longer than in the two other breeds (Cox regression, $P = 0.002$). A similar but less-strong ($P = 0.063$) effect of breed on time-to-first detection of trypanosomal antigen was found, whereas no breed effect was observed for clinical detection ($P = 0.432$). Sex had no effect in all detection systems. The TD varied between -56 and 115 (mean 28). Marked differences among breeds and between sexes were not observed (ANOVA, $P = 0.8$). We suggest that incidence studies are more suitable for detecting risk factors for animal trypanosomosis than prevalence-based (cross-sectional) studies because the latter often result in misinterpretation of factors that increase the survival time with infection as risk factors.

(c) TRYPANOTOLERANCE

[See also **24**: no. 11971]

(d) TREATMENT

[See also **24**: no. 11966]

11973 **Assefa, E. and Abebe, G., 2001.** Drug-resistant *Trypanosoma congolense* in naturally infected donkeys in north Omo Zone, southern Ethiopia. *Veterinary Parasitology*, **99** (4): 261-271.

Abebe: Faculty of Veterinary Medicine, Addis Ababa University, PO Box 34 Debre Zeit, Ethiopia.

A three-part study was conducted to determine the efficacy of isometamidium chloride in donkey populations naturally infected with trypanosomes in north Omo Zone, southern Ethiopia. In the first, 373 randomly selected donkeys from four villages were

examined for trypanosome infections by the dark ground/phase contrast buffy coat technique (BCT) in November 1999. The trypanosome prevalence was 18.2% (95% confidence interval (CI): 14.4, 22.5) and *Trypanosoma congolense* was the commonest species accounting for 66.2% of the overall infections. In the second part, 40 infected donkeys were selected and treated with a prophylactic dose of 1.0 mg/kg of isometamidium chloride and thereafter monitored every 14 days for 90 days. Trypanosomes were detected in eight donkeys within one month and in 20 donkeys within two months of treatment. About 16% (5/32) of donkeys infected with *T. congolense* were detected to be parasitaemic one month after treatment. In addition, the result also revealed that all relapse/breakthrough infections were due to *T. congolense*. In the third part of this study mice were infected with two *T. congolense* field isolates from donkeys that were found to be parasitaemic within one or two months after isometamidium treatment. The mice were treated with ranges of doses of isometamidium chloride or diminazene aceturate and thereafter followed for relapse infection. Isometamidium chloride at doses 0.5-4 mg/kg body weight and diminazene aceturate at doses of 3.5-28 mg/kg body weight failed completely to cure *T. congolense* infections in any of the mice.

11974 **Coles, G.C., 2001.** Control of trypanosomes in cattle. (Letter.) *Trends in Parasitology*, **17** (5): 219.

Coles: Department of Clinical Veterinary Sciences, University of Bristol, Langford House, Bristol, BS40 5DU, UK. [gerald.coles@bristol.ac.uk]

11975 **Fèvre, E., 2001.** More thoughts on the control of trypanosomes in cattle. (Letter.) *Trends in Parasitology* **17** (9): 412-413.

Fèvre: Centre for Tropical Veterinary Medicine, University of Edinburgh, Easter Bush, Roslin, Midlothian, EH25 9RG, UK. [eric.fevre@ed.ac.uk]

7. EXPERIMENTAL TRYPANOSOMIASIS

(a) DIAGNOSTICS

[See also **24**: no. 11968]

(b) PATHOLOGY AND IMMUNOLOGY

11976 **Barry, J.D. and McCulloch, R., 2001.** Antigenic variation in trypanosomes: Enhanced phenotypic variation in a eukaryotic parasite. (Review.) *Advances in Parasitology*, **49:** 1-70.

Barry: Wellcome Centre for Molecular Parasitology, University of Glasgow, 56 Dumbarton Road, Glasgow, G11 6NU, UK.

11977 **De Baetselier, P., Namangala, B., Noël, W., Brys, L., Pays, E. and Beschin, A., 2001.** Alternative versus classical macrophage activation during

experimental African trypanosomosis. [Mice, *T. congolense, T. brucei*.] *International Journal for Parasitology*, **31** (5-6): 575-587.

Beschin: Cellular Immunology Unit, Flemish Interuniversity Institute for Biotechnology, VIB-VUB, Paardenstraat 65, B-1640 St Genesius-Rode, Belgium. [abeschin@vub.ac.bc]

African trypanosomes are extracellular parasites causing sleeping sickness to human or nagana to livestock in sub-Saharan Africa. To gain insight into factors governing resistance/susceptibility to these parasites, the immune responses in mice infected with a *Trypanosoma brucei* phospholipase C null mutant ($PLC^{-/-}$) or its wild type counterpart (WT) were compared. We found that the *T. b. brucei* mutant inducing a chronic infection triggers the production of type I cytokines during the early stage of infection, followed by the secretion of type II cytokines in the late/chronic phase of the disease. In contrast, WT-infected mice are killed within 5 weeks and remain locked in a type I cytokine response. The type I/type II cytokine balance may influence the development of different subsets of suppressive macrophages, i.e. classically activated macrophages (type I) versus alternatively activated macrophages (type II) that are antagonistically regulated. Therefore, the phenotype and accessory cell function of macrophages elicited during WT and $PLC^{-/-}$ *T. b. brucei* infections were addressed. Results indicate that classically activated macrophages develop in a type I cytokine environment in the early phase of both WT and $PLC^{-/-}$ trypanosome infections. In the late stage of infection, only $PLC^{-/-}$ infected mice resisting the infection develop type II cytokine-associated alternative macrophages. In parallel, we found that mice susceptible to *T. congolense* infection, showing an exponential parasite growth until they die, have a higher level of type II cytokines in the early stage of infection than resistant animals controlling the first peak of parasitaemia. The levels of type I cytokines were comparable in both *T. congolense*-resistant and -susceptible mice. On the basis of these results, we propose that survival to African trypanosome infection requires a type I cytokine environment and classical macrophage activation in the early stage of infection, enabling mice to control the first peak of parasitaemia. Thereafter, a switch to type II cytokine environment triggering alternative macrophage activation is required to enable progression of the disease into the chronic phase. The possible role of the sequential activation of alternative macrophages in the late/chronic stage of infection in the increased resistance of mice to $PLC^{-/-}$ *T. b. brucei* will be discussed.

11978 **Iraqi, F., Sekikawa, K., Rowlands, J. and Teale, A., 2001.** Susceptibility of tumour necrosis factor-α genetically deficient mice to *Trypanosoma congolense* infection. *Parasite Immunology*, **23** (8): 445-451.

Teale: Institute of Aquaculture, University of Stirling, Stirling FK9 4LA, UK. [a.j.teale@stir.ac.uk]

The TNF-α gene on mouse chromosome MMU17 is among the candidates for the trypanosomosis resistance QTL *Tir1*. *Tir1* has the largest effect of those loci so far detected which influence degree of resistance to murine trypanosomosis caused by *Trypanosoma congolense* infection. We therefore studied the survival to 180 days after

challenge with *T. congolense* of mice that were homozygous and hemizygous with respect to a disruption of the TNF-α gene on a > 99% C57BL/6 (resistant) background. We also examined the responses of TNF-α hemizygous mice produced by crossing the deletion line with mice of the C57BL/6J strain, and with mice of the susceptible A/J strain. Mice lacking a functional TNF-α gene were shown to be highly susceptible to challenge with *T. congolense* with a median survival time of 37 days. This was comparable to 71 days for control wild-type mice, and 61 and 111 days for mice of the susceptible A/J and resistant C57BL/6J strains, respectively. In mice of the deletion line, the C57BL/6 TNF-α allele tended to be dominant to the TNF knockout in terms of resistance. We conclude that TNF-α plays an important role in resistance to the effects of *T. congolense* infection in mice.

(c) CHEMOTHERAPEUTICS

[See also **24**: no. 11966]

11979 **Brun, R., Burri, C. and Gichuki, C.W., 2001.** The story of CGP 40 215: studies on its efficacy and pharmacokinetics in African green monkey infected with *Trypanosoma brucei rhodesiense*. *Tropical Medicine and International Health*, **6** (5): 362-368.

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CGP 40 215 is an inhibitor of S-adenosylmethionine decarboxylase, a key enzyme in trypanosomal polyamine biosynthesis. It is highly active against *Trypanosoma brucei rhodesiense* and *T. b. gambiense in vitro* and in the corresponding rodent models, and therefore was a promising candidate for further development as a new drug against human African trypanosomiasis. We conducted initial pharmacokinetic and efficacy studies in African green monkeys based on two dose-finding studies, an infection-treatment and a pharmacokinetic study in eight monkeys infected with *T. b. rhodesiense* in the 1st stage of infection. PK analysis revealed curative drug levels in the serum but complete absence of the drug in the cerebrospinal fluid. No adverse effects of the drug were observed, although in rats CGP 40 215 had caused hypotension. The following PK parameters were calculated using a two-compartment model: $t_{1/2}$ = 1.8 h, V_{ss}/f = 0.4 l/kg, CL/f = 3.0 ml/min × kg and AUC = 21 900 ng × h/ml. Six of the eight monkeys were cured, one animal relapsed on day 222 and one animal died of unknown reasons, but was aparasitaemic. The study confirmed the curative potential of CGP 40 215 for 1st stage *T. b. rhodesiense* infection. Unfortunately, it was also found that the compound did not pass the blood-brain barrier, a prerequisite for cure of 2nd stage (CNS) infection. As the majority of sleeping sickness patients seeking treatment are in the 2nd stage of the disease, further development of the compound was stopped.

11980 **Cano, M.I.N., 2001.** Telomere biology of trypanosomatids: more questions than answers. [Incl. *T. brucei*]. *Trends in Parasitology*, **17** (9): 425-429.

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Trypanosomatids are severe pathogens in developing countries, where they affect both humans and domestic animals. Factors intrinsic to the host, the toxicity or subcurative effects of the available antiparasite medication and the low perspective of potential vaccines favor research on novel candidates for drug target. Telomeres are essential for the survival of most eukaryotes. In trypanosomatids, events such as antigenic variation and/or gene conversion and duplication occur at telomeric positions, possibly facilitating genome rearrangement. Understanding the role that telomere maintenance might play in the cell life span of trypanosomatids has important implications for therapeutics of parasitic diseases.

11981 **Keiser, J. and Burri, C., 2001.** Evaluation of quinolone derivatives for antitrypanosomal activity. *Tropical Medicine and International Health*, **6** (5): 369-389.

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About 160 fluoroquinolones and derivatives were tested for antitrypanosomal activity in a drug sensitivity assay followed by fluorometric evaluation. The most active quinolone compounds had IC_{50} values in the range from 100 to 900 ng/ml, while several derivatives were not active at a concentration of 100 µg/ml. In a structure activity relationship study, modification of the quinolones at position R1, R2, R3 and R8 did not influence trypanocidal activity. An exchange of the fluor at position 6 may contribute to an increase in activity but does not entirely control it. Pyrrolidine substituents at position R7 generally were more active than other substituents at this position. Tetracyclic quinolone derivatives were amongst the most active compounds with IC_{50} values in the range of 0.3-8.8 µg/ml. The *in vitro* cytotoxicity on HT-29 cells was determined for active compounds with IC_{50} values below 1 µg/ml. In addition, six drugs with an IC_{50} below 1 µg/ml and a selectivity index of more than 10 were chosen for *in vivo* experiments. Dose escalation experiments with a maximum dose of 100 mg/kg/bid were performed in a mouse model without central nervous system involvement. For unknown reasons the *in vitro* effect of the drugs could not be confirmed *in vivo*, but the class of compound remains of interest for their mode of action, the low toxicity, pharmacological properties and the availability of a large number of synthesized compounds.

11982 **Loiseau, P.M., Gutierrez-Rios, M.T., De Frutos, M.I. and Craciunescu, D.G., 2001.** Structure-activity relationships for new organometallic complexes active against bloodstream forms of *Trypanosoma brucei brucei*. (Short communication.) *Parasitology Research*, **87** (7): 566-569.

Loiseau: Biologie et Contrôle des Organismes Parasites, UPRES 398-IFR 75, Faculté de Pharmacie, Université de Paris-Sud, 92290 Chatenay-Malabry Cédex, France. [Philippe.Loiseau@cep.u-psud.fr]

11983 **Namangala, B., Noël, W., De Baetselier, P., Brys, L. and Beschin, A., 2001.** Relative contribution of interferon-γ and interleukin-10 to resistance to murine African trypanosomosis. *Journal of Infectious Diseases*, **183** (12): 1794-1800.

Beschin: Cellular Immunology Unit, Flemish Interuniversity Institute for Biotechnology, VIB-VUB, Paardenstr. 65, B-1640 St-Genesius-Rode, Belgium. [abeschin@vub.ac.be]

Resistance to *Trypanosoma brucei brucei* has been correlated with the ability of infected animals to produce interferon (IFN)-γ and tumor necrosis factor (TNF) in an early phase of infection, followed by interleukin (IL)-4 and IL-10 in late and chronic stages of the disease. Contributions of IFN-γ and IL-10 in the control of parasitemia and survival of mice infected with *T. brucei brucei* were investigated by using IFN-$\gamma^{-/-}$ and IL-$10^{-/-}$ mice. Results suggest that IFN-γ, mainly secreted by $CD8^+$ T cells, is essential for parasite control via macrophage activation, which results in TNF and nitric oxide secretions. IL-10, partially secreted by $CD4^+$ T cells, seems to be important for the survival of infected mice. Its absence resulted in the sustained secretion of inflammatory mediators, which indicated the role of IL-10 in maintaining the balance between pathogenic and protective immune responses during African trypanosomosis.

11984 **Opperdoes, F.R. and Michels, P.A.M., 2001.** Enzymes of carbohydrate metabolism as potential drug targets. [*T. brucei*]. *International Journal for Parasitology*, **31** (5-6): 482-490.

Opperdoes: Christian de Duve Institute of Cellular Pathology, ICP-TROP 74/39, Avenue Hippocrate 74, B-1200 Brussels, Belgium. [opperdoes@trop.ucl.ac.be]

The potential for chemotherapeutic exploitation of carbohydrate metabolism in the Trypanosomatidae is reviewed. This review is based largely on discussions held at a meeting of the COST B9 Action, entitled 'Bioenergetics of Protozoan Parasites'. The major questions posed were: which enzymes are the best to target; what further information is required to allow their use for rational drug development; what compounds would constitute the best inhibitors and which of the enzymes of the pentose-phosphate pathway are present inside the glycosomes, as well? Only partial answers could be obtained in many cases, but the interactive discussion between the multidisciplinary group of participants, comprising chemists, biochemists and molecular biologists, provided thought-provoking ideas and will help direct future research.

11985 **Raper, J., Portela, M.P.M., Lugli, E., Frevert, U. and Tomlinson, S., 2001.** Trypanosome lytic factors: novel mediators of human innate immunity. (Review.) *Current Opinion in Microbiology*, **4** (4): 402-408.

Raper: Department of Medical and Molecular Parasitology, New York, University School of Medicine, 341 East 25th Street, New York, USA.

A novel trypanosome lytic factor (TLF) has been characterized that protects humans from infection by *Trypanosoma brucei brucei*. The mechanism of trypanolysis is unknown; contrary to one hypothesis, TLF does not kill trypanosomes by generating oxygen radicals. However, these trypanosomes become human-infective when they express a serum-resistance-associated gene.

8. TRYPANOSOME RESEARCH

(a) CULTIVATION OF TRYPANOSOMES

[See also **24**: no. 11958]

(b) TAXONOMY, CHARACTERISATION OF ISOLATES

[See also **24**: no. 11965]

11986 **Alsford, S., Wickstead, B., Ersfeld, K. and Gull, K., 2001.** Diversity and dynamics of the minichromosomal karyotype in *Trypanosoma brucei*. *Molecular and Biochemical Parasitology*, **113** (1): 79-88.

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The genome of African trypanosomes contains a large number of mini-chromosomes. Their only proposed role is in the expansion of the parasites' repertoire of telomeric variant surface glycoprotein (VSG) genes as minichromosomes carry silent VSG gene copies in telomeric locations. Despite their importance as VSG gene donors, little is known about the actual composition of the minichromosomal karyotype and the stability of its inheritance. In this study we show, by using high-resolution pulsed-field electrophoresis, that a non-clonal trypanosome population contains an extremely diverse pattern of minichromosomes, which can be resolved into less complex clone-specific karyotypes by non-selective cloning. We show that the minichromosome patterns of such clones are stable over at least 360 generations. Furthermore, using DNA markers for specific minichromosomes, we demonstrate the mitotic stability of these mini-chromosomes within the population over a period of more than 5 years. Length variation is observed for an individual minichromosome and is most likely caused by a continuous telomeric growth of approximately 6 bp per telomere per cell division. This steady telomeric growth, counteracted by stochastic large losses of telomeric sequences is the most likely cause of minichromosome karyotype heterogeneity within a population.

11987 **Bringaud, F., Biteau, N., Donelson, J.E. and Baltz, T., 2001.** Conservation of metacyclic variant surface glycoprotein expression sites among different trypanosome isolates. [*T. brucei*.] *Molecular and Biochemical Parasitology*, **113** (1): 67-78.

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We identified in a *Trypanosoma brucei brucei* strain (AnTat 1) an expression site for a metacyclic variant surface glycoprotein (MVSG) gene (*MVSG*) that was previously characterized in a *T. b. rhodesiense* strain (WRATat 1.1). The 3.4 kb sequences of the two expression sites are 99.6% identical, with no differences in the sequence of the 1.5 kb MVSG. Two other MVSGs in the WRATat 1.1 genome are not present in the AnTat 1 genome. In addition, five other *T. b. brucei* and *T. b. rhodesiense* strains, isolated in the same geographic region as the two former strains, do not contain any of these three MVSGs. Two of these five strains, however, appear to possess a very similar MVSG expression site, but with different MVSGs in it. Thus, the presence of the same MVSG in the same expression site in two different isolates is unusual and may be the result of genetic exchange in the field between *T. b. brucei* and *T. b. rhodesiense* isolates. Analysis of other African trypanosome strains for the presence of the three WRATat 1.1 MVSG expression sites demonstrated that the expression sites' promoter sequences are much more likely to be present than are specific MVSGs suggesting that loss of MVSGs is the result of replacement by other MVSGs. The promoter region of the MVSG expression site active in the WRATat 1.1 MVAT7 variant was found to be highly conserved among *T. b. brucei*, *T. b. rhodesiense* and *T. b. gambiense* group 2 isolates, whereas it does not occur in the *T. b. gambiense* group 1 isolates tested. A phylogenetic analysis of this promoter region sequence shows that the *T. b. gambiense* group 2 isolates form a monophyletic clade well separated from the *T. b. brucei*/*T. b. rhodesiense* isolates. Thus, whilst the *T. b. brucei*, *T. b. rhodesiense* and *T. b. gambiense* group 2 isolates are closely related but heterogenous, molecular tools may be developed to distinguish *T. b. gambiense* group 2 isolates from the others.

11988 **Gibson, W., 2001.** Molecular characterization of field isolates of human pathogenic trypanosomes. [*T. brucei* subspecies] *Tropical Medicine and International Health*, **6** (5): 401-406.

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The accurate identification of each of the three subspecies of *Trypanosoma brucei* remains a challenging problem in the epidemiology of sleeping sickness. Advances in molecular characterization have revealed a much greater degree of heterogeneity within the species than previously supposed. Only group 1 *T. b. gambiense* stands out as a separate entity, defined by several molecular markers. *T. b. rhodesiense* is generally too similar to sympatric *T. b. brucei* strains to be distinguished from them by any particular molecular markers. Nevertheless, characterization of trypanosome isolates from humans and other animals has allowed the identification of potential reservoir hosts of *T. b. rhodesiense*. The recent discovery of a gene for human serum resistance may provide a useful marker for *T. b. rhodesiense* in the future. There have been few attempts to find associations between genetic markers and other biological characters, except human

infectivity. However, virulence or fly transmissibility have been correlated with molecular markers in some instances.

11989 **Gibson, W., 2001.** Sex and evolution in trypanosomes. [*T. brucei.*] *International Journal for Parasitology*, **31** (5-6): 643-647.

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Trypanosoma brucei is still the only kinetoplastid known to undergo genetic exchange, but it seems unreasonable to suppose that it evolved this process all by itself. The position of *T. brucei* on a molecular phylogenetic tree constructed from 18S ribosomal RNA gene sequences offers no clues to the likely existence of genetic exchange in trypanosome species other than the Salivaria, because this group of trypanosomes appears to have diverged from the rest a very long time ago. Antigenic variation is one characteristic shared by the Salivaria, which has been particularly well-studied in *T. brucei*. The large proportion of the genome devoted to variant antigen genes and related sequences in *T. brucei* suggests a possible role for genetic exchange in enhancing the diversity of the repertoire. Alternatively, genetic exchange may counter potential excessive double-strand DNA damage brought about by the DNA rearrangements associated with antigenic variation. The remarkable biparental inheritance of organelle DNA (= kinetoplast DNA) in *T. brucei* is without precedent in other eukaryotes. The result of genetic exchange is to enhance the heterogeneity of the kinetoplast DNA minicircles.

11990 **Gull, K., 2001.** The biology of kinetoplastid parasites: insights and challenges from genomics and post-genomics. [*T. brucei*.] *International Journal for Parasitology*, **31** (5-6): 443-452.

Gull: School of Biological Sciences, University of Manchester, 2.205 Stopford Building, Oxford Road, Manchester M13 9PT, UK. [k.gull@man.ac.uk]

Kinetoplastid parasites exhibit a rich and diverse biology which mirrors many of the most interesting topics of current interest and study in the broader biological sciences. These evolutionarily ancient organisms possess intriguing mechanisms for control of gene expression, and exhibit complex patterns of cell morphogenesis orchestrated by an internal cytoskeleton. Their cell shapes change during a set of complex cell type differentiations in their life cycles. These differentiations are intimately linked to interactions with mammalian hosts or insect vectors, and often, these differentiations appear central to the successful transfer of the parasite between vector and host, and host and vector. The basics of this rich and complex cell and life cycle biology were described (with often rather forgotten clarity and prescience) in the early period of the last century. The last 30 years have seen major developments in our understanding of this biology. Ultrastructural differences in the various cells of the life cycle stages of *Trypanosoma brucei*, *T. cruzi* and the various *Leishmania* species have been documented, and such studies have proven highly informative in defining important aspects of parasite adaptation. They have also proven to be a rich source of information for defining unusual aspects of parasite cell

biology, novel organelles and cell architecture. This ultrastructural cell biology has been mirrored in a set of biochemical explanations defining unusual aspects of metabolism, surface molecules, and organelles. Finally, the application of molecular biology to these parasites revealed fascinating layers of complexity in the control of gene expression. These molecular studies have given us particular insights into polycistronic transcription, trans-splicing, RNA editing and gene rearrangements during antigenic variation. In contrast to other microbial systems, these cell biological, biochemical and molecular studies have not been greatly aided by insights gained from genetics - the diploid nature of the genome has discouraged the application of selectional genetics, mutant isolation and analysis. This is an important fact, since in general, it means that we have only recently started to analyse the phenotypes of mutants produced in the context of reverse genetics. It is argued that this lack of investment in the analysis of mutant phenotype is just one of the challenges that will need to be met if we are to gain the expected added value from the parasite genome projects. In this presentation, some of the current areas of interest in the biology of *T. brucei*, *T. cruzi* and the *Leishmania* species will be used to rehearse some of the insights and challenges that are likely to stem from the application of genomics and post-genomic studies to the kinetoplastid parasites. The presentation slants towards *T. brucei* biology; but generalities of application to other kinetoplastid parasites should be apparent.

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Overath: Max-Planck-Institut fur Biologie, Abteilung Membranbiochemie, Correnstrasse 38, D-72076 Tubingen, Germany. [peter.overath@ tuebingen.mpg.de]

Molecular phylogenetic analysis using genes coding for ribosomal RNA and proteins suggests that trypanosomes are monophyletic. Salivarian trypanosomes showing antigenic variation of the variant surface glycoprotein (VSG) diverged from non-salivarian trypanosomes some 200-300 million years ago. Representatives of the non-salivarian group, the mammalian parasite, *Trypanosoma cruzi*, and the freshwater fish trypanosome, *T. carassii*, are characterised by surfaces dominated by carbohydrate-rich mucin-like glycoproteins, which are not subject to antigenic variation. It is suggested that this latter surface structure is typical for non-salivarian trypanosomes as well as members of the other kinetoplastid suborder, the Bodonina. This would imply that at some point in time in the evolution of the Salivaria the highly abundant and comparatively poorly immunogenic mucin-like molecules must have been replaced for equally abundant but highly immunogenic VSG-like molecules. While the selective advantage for such a unique transition is difficult to imagine, the subsequent diversification of VSG genes/molecules may have been comparatively straightforward because even the most limited form of antigenic variation would have extended the duration of infection in the vertebrate and thus would have increased the chance for transfer to the vector.

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[See also **24**: nos. 11951, 11952, 11985]

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Bangs: Department of Medical Microbiology and Immunology, University of Wisconsin – Madison Medical School, 1300 University Avenue, Madison, WI 53706, USA. [jdbangs@facstaff.wisc.edu]

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