

Reports on Individual Drugs

Artemether in children with severe malaria

With the rapid incursion of chloroquine-resistant falciparum malaria into the hyperendemic areas of West Africa and ominous indications that the prevalence of strains resistant to quinine is increasing in south-east Asia and South America, there is an urgent need for alternative treatment for severe malaria. Fortunately, clinical experience with artemisinin and its derivatives in China (1, 2), and subsequently in Vietnam (3) and Myanmar (4), has been consistent in confirming their promise as potent antimalarials that seem to reduce parasitaemia more rapidly than other antimalarial drugs.

This experience has now been reinforced by a demonstration that artemether (a water soluble hemisuccinate derivative of artemisinin) is a well tolerated and rapidly effective parenteral treatment for severe malaria in children (5). Forty-three Gambian children aged from 2 to 12 years were studied. All had severe malaria and 19 were in unrousable coma on admission. They were randomized to receive intramuscularly either artemether suspended in groundnut oil using a loading dose of 4 mg/kg followed by 2 mg/kg every 24 hours, or chloroquine sulfate 3.5 mg base/kg every 6 hours. The median duration of parenteral antimalarial treatment was 24 hours in both groups and no patient received more than 3 doses of artemether. Time to parasite clearance and resolution of fever was similar in both groups, and there was no evidence of either systemic or local adverse effects. In all, 8 patients died of whom 6 were receiving chloroquine. The authors emphasize, however, that much larger comparative studies will need to be completed before it can be determined whether or not artemisinin compounds can save more lives than chloroquine or quinine administered in appropriate doses.

Artemether, in particular, has characteristics that favour its use in field conditions. Its slow absorption from the injection site allows once daily dosing; it is well tolerated on intramuscular injection; and it does not degrade readily on storage. Further experience is necessary, however, before its potential as a

first-line treatment of severe malaria in rural clinics and health centres can be defined with certainty.

References

1. Qinghaosu Antimalarial Coordinating Research Group. Antimalarial studies on qinghaosu. *Chinese Medical Journal*, **92**: 811-816 (1979).
2. Li, Q., Guo, X., Jiang, R. Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives. *Journal of Traditional Chinese Medicine*, **2**: 125-130 (1982).
3. Arnold, K., Hien, T., Chinh, N. et al. A randomised comparative study of artemisinin (Qinghaosu) suppositories and oral quinine in acute falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **84**: 499-502 (1990).
4. Pe Than Myint, Tin Shwe. The efficacy of artemether (qinghaosu) in *Plasmodium falciparum* and *P. vivax* in Burma. *South-east Asian Journal of Tropical Medicine and Public Health*, **17**: 19-22 (1986).
5. White, N., Waller, D., Crawley, J. et al. Comparison of artemether and chloroquine for severe malaria in Gambian children. *Lancet*, **339**: 317-321 (1992).

IUDs and pelvic inflammatory disease: a reassuring assessment

The possibility that intrauterine devices (IUDs) might be associated with a risk of pelvic inflammatory disease (PID) has been appreciated from the time that they were first introduced some 30 years ago. Assessments conducted on the essentially mechanical devices available during the late 1960s were, in general, reassuring (1, 2). Whereas modest correlations were apparent, many of the infections were regarded as minor insofar that they were treated, apparently effectively, without removing the IUD. During the 1970s, however, increasing use of IUDs in North America and western Europe was concurrent with a marked increase in the incidence of PID. Early controlled studies fuelled speculation that these trends were causally related (3, 4). In the United States, in particular, the use of IUDs decreased by more than two-thirds as a consequence of this concern (5) and two companies decided to withdraw their products from the market.

With hindsight, it seems that the magnitude of the risk was generally overstated (6). Disproportionate attention was focused on the performance of the Dalkon Shield, which was associated with a higher risk of PID than other devices (7), while the contribution of other factors to the rising incidence of PID, notably the prevalence of sexually transmitted diseases, was underestimated (8). Reanalysis of one study has indicated that, among women who are at low risk of sexually transmitted disease, use of an IUD carries virtually no excess risk of PID (9).

Given this history, a need clearly exists to assess the risks associated with currently used devices. Data obtained within a series of prospective efficacy studies coordinated by WHO (10, 11) has created a unique opportunity to accomplish this. In all, information on some 23 000 insertions and more than 50 000 years of use by women largely in the Americas, Asia and Europe was analysed (12). The results confirm that, once the devices have been in place for several weeks, modern copper-releasing IUDs are associated with a rate of PID — as defined on clinical criteria — of only some 1.6 cases per 1000 years of follow-up over periods extending up to 8 years. Indeed, among women at remote risk of sexually transmitted disease, no excess risk of PID was discernible. In contrast, during the 3 week post-insertion period, the incidence of PID peaked transiently by some 6-fold within the cohort as a whole, whereas even higher risks were evident within specific geographical areas, among older recipients, and among women at enhanced risk of sexually transmitted disease.

These results not only underscore the need to ensure careful preliminary assessment of patients and strict asepsis when IUDs are fitted; they reopen the question of whether, in some circumstances, IUDs should be inserted under antibiotic cover (13) and they offer support to the principle that, in the absence of complications, devices should preferably be left in place for the duration of their labelled lifespan (14).

References

1. World Health Organization. *IUDs: physiological and clinical aspects*. WHO Technical Report Series, No. 397 (1968).
2. Advisory Committee on Obstetrics and Gynecology. *Report on IUDs*. US Food and Drug Administration, Washington, DC, 1968.
3. Wright, N., Leemle, P. Acute PID in an indigent population. *American Journal of Obstetrics and Gynecology*, **101**: 979-990 (1968).
4. Westrom, L., Bengtsson, L., Mardh, D. The risk of pelvic inflammatory disease in women using intrauterine contraceptive devices as compared to non-users. *Lancet*, **2**: 221-224 (1976).
5. Mosher, W., Pratt, W. Use of contraception and family planning services in the United States, 1988. *American Journal of Public Health*, **9**: 1132-1133 (1990).
6. Struthers, B. IUDs, PID and fertility in nulliparous women. *Advances in Contraception*, **7**: 211-230 (1990).
7. Kessel, E. Pelvic inflammatory disease with intrauterine device use: a reassessment. *Fertility and Sterility*, **51**: 1-11 (1989).
8. Lee, N., Rubin, G., Grimes, D. Measures of sexual behaviour and the risk of pelvic inflammatory disease. *Obstetrics and Gynecology*, **77**: 425-430 (1991).
9. Lee, N., Rubin, G., Ory, H., Burkman, R. Type of intrauterine device and risk of pelvic inflammatory disease. *Obstetrics and Gynecology*, **62**: 1-6 (1983).
10. World Health Organization. Interval IUD insertion in parous women: a randomized multicentre comparative trial of the Lippes Loop D, TCu220C, and the copper 7. *Contraception*, **26**: 1-2 (1982).
11. World Health Organization. Task Force on Safety and Efficacy of Fertility Regulation Methods. The TCu380A, TCu220C, Multiload 250 and Nova T IUDs at 3, 5 and 7 years of use: results from three randomized multicentre trials. *Contraception*, **42**: 141-158 (1990).
12. Farley, T., Rosenburg, M., Rowe, P. et al. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet*, **339**: 785-788 (1992).
13. Sinei, S., Schulz, K., Lamptey, P. et al. Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion. *British Journal of Obstetrics and Gynaecology*, **97**: 412-419 (1990).
14. Newton, J., Tacchi, D. Long-term use of IUDs. *Lancet*, **335**: 1322-1323 (1990).

Leprosy: interim appraisal of an *M. leprae* vaccine

More than 5 million new cases of leprosy are still identified globally each year and, with the widespread emergence of dapson resistance, chemotherapy has become both costly and complicated. It is estimated that no more than half the infected patients benefit from full courses of oral multidrug therapy currently recommended by WHO (1). Effective immunization appears to be an attainable

goal since BCG vaccine provides substantial protection in some areas. Elsewhere, however, and for reasons that remain uncertain, its performance has been disappointing (2).

Clinical leprosy is widely presumed to result from an impaired antigen-specific immune response to infection (3). Expectation has consequently been aroused that a vaccine containing killed *Mycobacterium leprae* in addition to BCG might be more effective in stimulating an immune response in patients with preexisting subclinical infections. Indeed, favourable immunological changes and amelioration of symptoms have been reported in a substantial proportion of patients with lepromatous and indeterminate leprosy who have been immunized with the combined vaccine (4, 5). None the less, 5-year follow-up in Venezuela of almost 30 000 contacts who were immunized either with BCG alone or in combination with 6×10^8 irradiated, autoclaved *M. leprae* purified from the tissues of infected armadillos has provided no evidence at this stage that the latter offers significantly better protection than BCG alone (6).

Clinical signs of leprosy have thus far developed in 59 patients within the cohort. Of these, 31 had been vaccinated with BCG alone and 28 with the combined vaccine. In most of these cases, however, infection is likely to have antedated vaccination. Surveillance of the group will need to be maintained for a further 10 years before the majority of new cases can be confidently attributed to postvaccination infection. Meanwhile, retrospective analysis of BCG scars on patients who were admitted to the study and those who were excluded because of evidence of leprosy on presentation suggest that BCG alone reduces the risk of infection by some 50% and that the degree of this protection is increased by subsequent booster doses.

References

- Noordeen, S. A look at world leprosy. *Leprosy Reviews*, **62**: 72-86 (1991).
- Fine, P. BCG vaccination against tuberculosis and leprosy. *British Medical Bulletin*, **44**: 691-703 (1988).
- Convit, J., Pinaridi, M., Arias Rojas, F. Some considerations regarding the immunology of leprosy. *International Journal of Leprosy*, **30**: 556-564 (1971).
- Convit, J., Aranzazu, N., Pinaridi, M., Ulrich, M. Immunological changes observed in indeterminate and lepromatous leprosy patients and Mitsuda-negative contacts after the inoculation of a mixture of *Mycobacterium leprae* and BCG. *Clinical and Experimental Immunology*, **36**: 214-220 (1971).
- Convit, J., Ulrich, M., Aranzazu, N. et al. The development of a vaccination model using two microorganisms and its application in leprosy and leishmaniasis. *Leprosy Reviews*, **57**(suppl 2): 263-273 (1986).
- Convit, J., Sampson, C., Zúñiga, M. Immunoprophylactic trial with combined *Mycobacterium leprae*/BCG vaccine against leprosy: preliminary results. *Lancet*, **339**: 446-450 (1992).

Quinine: use of loading doses in falciparum malaria

The aim in using intravenous quinine to treat patients with falciparum cerebral malaria is to attain effective blood concentrations as rapidly as possible without inducing serious drug toxicity. Use of a rapidly-infused initial loading dose was first advanced on the basis of a study undertaken in south-east Asia over ten years ago (1). However, since there is little margin between the therapeutic and toxic dose of quinine, the practice has remained controversial (2), not least because of concern that dangerously high concentrations might occur in acutely ill young children if the volume of distribution of the drug were reduced (3), and also because it is rarely possible under field conditions to establish whether the patient has taken quinine orally.

None the less, because severe chloroquine-resistant malaria is being encountered with increasing frequency throughout equatorial Africa (4), the need to reappraise both the safety and the efficacy of parenteral quinine therapy within the African context has become urgent. The possibility has been raised that African strains of *Plasmodium falciparum* may be more sensitive to quinine than south-east Asian strains (5). Moreover, because prolonged and repeated intravenous infusions are often impracticable in the rural African setting, the safety of intramuscular administration needs to be established. Two groups have already placed relevant experience on record (5, 6).

The first of these compared the standard regimen used locally in Cameroon — 8 mg base/kg over 8 hours, three times daily for 3 days — with a regimen in which an additional loading infusion of 8 mg base/kg was administered during the first hour of treatment (5). Ten patients in unrousable coma and with *P. falciparum* parasitaemia ($> 2000/\mu\text{l}$) were allocated at random to each treatment. All patients were discharged fully recovered 3 days after admission, but the length of coma and the

parasite clearance time were significantly reduced among those who received the loading dose.

The second study provides a comparison of the pharmacokinetics and clinical effectiveness of three regimens in a group of 59 children with severe malaria: high dose intravenous or intramuscular quinine — 16 mg base/kg initially, followed by 8 mg/kg every 12 hours — and low dose intravenous quinine — 8 mg base/kg followed by 4 mg/kg every 12 hours. The 12-hour dosing interval was selected as being more practicable under field conditions than the usual 8-hour interval. Blood concentrations of quinine resulting from each of these regimens consistently exceeded the 99% *in vitro* inhibitory concentration of quinine for 60 locally obtained isolates of *P. falciparum*. None the less, the higher dose regimens resulted in faster rates of parasite clearance and of clinical response.

The application of pharmacokinetic principles to the assessment of antimalarial treatment places the results of small-scale clinical trials on a much sounder basis. However, to assess the safety of therapeutic intervention on trials primarily designed to establish efficacy is far from adequate. Quinine has a narrow therapeutic index. Monitoring of far larger numbers of treated cases will be needed to establish with reasonable confidence whether a loading dose can be administered safely where there is no recourse to tertiary care facilities.

References

1. White, N., Looareesuwan, S., Warrell, D. et al. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *American Journal of Medicine*, **73**: 564-572 (1982).
2. Hall, A. Dangers of high dose quinine and over-hydration in severe malaria. *Lancet*, **1**: 1453-1454 (1985).
3. Shann, F., Stace, J., Edstein, M. Pharmacokinetics of quinine in children. *Journal of Pediatrics*, **106**: 506-510 (1985).
4. Hengy, C., Jambou, R., Eberle, F et al. Problèmes thérapeutiques posés par la chimiorésistance de *P. falciparum* aux antimalariques à Yaoundé, Cameroun. Abstracts of the VII International Congress of Parasitology, Paris. *Bulletin de la Société Française de Parasitologie*, **8** (suppl. 1): 430 (1990).
5. Pasvol, G., Newton, C., Winstanley, P. et al. Quinine treatment of severe falciparum malaria in African children: a randomized comparison of three regimens. *American Journal of Tropical Medicine and Hygiene*, **45**: 702-713 (1991).
6. Fargier, J., Louis, F., Cot, M. et al. Reduction of coma by quinine loading dose in falciparum cerebral malaria. *Lancet*, **338**: 896-897 (1991).

More new experience with oral and parenteral typhoid vaccines

It has recently been estimated that, globally, some 30 million cases of typhoid fever occur each year (1) and that the mortality rate in some areas approaches 3% (2). For many years immunization against the disease was dependent upon parenteral administration of inactivated whole-cell preparations. These provide a measure of protection which has been estimated to range in different settings, predominantly in eastern Europe, from about 50% to 90% (3-8). However, because they frequently cause both local and systemic adverse reactions, they have not been used extensively in some areas where the disease is most highly endemic (9, 10).

Over the past decade two other types of vaccine have been developed. One is a parenterally administered capsular polysaccharide vaccine which induces antibodies to the Vi antigen of *Salmonella typhi* (11). The other, known as Ty21a, is a live attenuated non-pathogenic strain of *S. typhi* which can be administered orally (12). This lacks the Vi capsular polysaccharide and, although it induces other antibodies, it is thought to act primarily through induction of protective cell-mediated immunity (13, 14).

The Vi vaccine has been estimated to protect some 60 to 70% of adults and children over periods of observation extending from one to two years (15, 16). Results obtained with Ty21a have been more variable. A liquid formulation protected 88% of adult volunteers in the USA against challenge (17) and, throughout a three-year field study undertaken in Egypt, 3 doses of a similar formulation was 96% efficacious among 6 and 7 year-old children (18). However, lower levels of protection have since been recorded from Chile and Indonesia where the disease has higher prevalence (19-22). It seems that the intensity of many of the infections may have overwhelmed any vaccine-induced protective immunity.

Candidate live oral vaccines that produce Vi antigen are also now under development. These are prepared by recombinant DNA techniques rather than chemical mutagenesis, as is the case with TY21a. The objective is to produce a vaccine

that is more consistently efficient than any of the existing oral and parenteral preparations. At present, the Vi vaccine holds important advantage notwithstanding the need for parenteral administration. It is less expensive and much less costly to deliver since it is extremely stable, it requires no cold chain and is fully effective in a single dose.

References

- Institute of Medicine. Diseases of importance in developing countries. In: *New vaccine development; establishing priorities, vol II*. National Academy Press, Washington, 1986.
- Budiarso, R., Putrali, J., Muchtarrudin, R. et al. *Household survey 1986, Jakarta*. Department of Health, Indonesia, 1986.
- Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of phenol and alcohol typhoid vaccines. *Bulletin of the World Health Organization*, **26**: 357-369 (1962).
- Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of acetone-dried and inactivated and heat phenol-inactivated typhoid vaccines in Yugoslavia. *Bulletin of the World Health Organization*, **30**: 623-630 (1964).
- Hejfec, L., Salmin, L., Leitman, M. et al. A controlled field trial and laboratory study of five typhoid vaccines in the USSR. *Bulletin of the World Health Organization*, **34**: 321-339 (1966).
- Polish Typhoid Committee. Controlled field trials and laboratory studies on effectiveness of typhoid vaccines in Poland 1961-1964. *Bulletin of the World Health Organization*, **34**: 221-222 (1966).
- Ascroft, M., Singh, B., Nicholson, V. et al. A seven-year field trial of two typhoid vaccines in Guyana. *Lancet*, **2**: 1056-1060 (1967).
- Tapa, S., Cvjetanovic, B. Controlled field trial on the effectiveness of one and two doses of acetone-inactivated and dried typhoid vaccine. *Bulletin of the World Health Organization*, **52**: 75-80 (1975).
- Darmowigoto, R., Hoffman, S., Soeprawoto, I. et al. *Typhoid and paratyphoid fever in Plaju, Sumatra, 1978-1993*. Proceedings of the 11th International Congress for Tropical Medicine and Malaria, Calgary, Canada, 16-22 September, 1984, p. 193.
- Simanjuntak, C., Hoffmann, S., Punjabi, N. et al. Epidemiology of typhoid fever in a semiurban area, Paseh, West Java. *Cermin Dunia Kedokteran*, **45**: 16-18 (1987).
- Landy, M. Studies in Vi antigen. VI. Immunization of human beings with purified Vi antigen. *American Journal of Hygiene*, **60**: 52-62 (1954).
- Germania, R., Furer, E. Isolation and characterization of gal E mutant Ty21a of *Salmonella typhi*: a candidate strain for a live oral typhoid vaccine. *Journal of Infective Diseases*, **131**: 553-558 (1975).
- Tagliabue, A., Nencione, L., Caffarena, A. et al. Cellular immunity against *Salmonella typhi* after live vaccine. *Clinical and Experimental Immunology*, **62**: 242-247 (1985).
- Tagliabue, A., Villa, L., De Magistris, M. et al. IgA-driven cell-mediated antibacterial immunity in man after live oral Ty21a vaccine. *Journal of Immunology*, **137**: 1504-1510 (1986).
- Acharya, I., Lowe, C., Thapa, R. et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*. *New England Journal of Medicine*, **317**: 1101-1104 (1987).
- Klugman, K., Gilbertson, I., Koomhof, H. et al. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. *Lancet*, **2**: 1165-1169 (1987).
- Homick, R., Du Pont, H., Levine, M. et al. Efficacy of a live oral typhoid vaccine in human volunteers. *Development of Biological Standards*, **33**: 89-92 (1976).
- Wahdan, M., Serie, C., Cerisier, Y. et al. A controlled field trial of live *Salmonella typhi* strain Ty21a oral vaccine against typhoid: three year results. *Journal of Infectious Diseases*, **145**: 292-295 (1982).
- Levine, M., Ferreccio, C., Black, R., Germanier, R., Chilean Typhoid Committee. Large scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. *Lancet*, **1**: 1049-1052 (1987).
- Ferreccio, C., Levine, M., Rodriguez, H., Contreras, R., Chilean Typhoid Committee. Comparative efficacy of two, three or four doses of Ty21a live oral typhoid vaccine in enteric coated capsules. A field trial in an endemic area. *Journal of Infectious Diseases*, **159**: 766-769 (1989).
- Simanjuntak, C., Paleologo, F., Punjabi, N. et al. Oral immunization against typhoid fever in Indonesia with Ty21a vaccine. *Lancet*, **338**: 1055-1059 (1991).
- Levine, M., Ferreccio, C., Cryz, S., Ortiz, E. Comparison of enteric-coated capsules and liquid formulation of Ty21a typhoid vaccine in a randomized controlled field trial. *Lancet*, **336**: 891-894 (1990).

Vitamin A supplements and childhood mortality: further encouraging evidence

Over the past 10 years evidence has accumulated that vitamin A deficiency places young children at risk not only from xerophthalmia (1) but also from increased vulnerability to respiratory disease, protracted diarrhoea and potentially severe infectious illnesses, including measles (2-5). With one outstanding but unexplained exception (6), community trials in areas where deficiency is endemic have shown that vitamin A supplements administered at daily or weekly intervals reduce early childhood mortality by one-third to one-half (7-9).

A further randomized, double-blind, controlled community trial which involved almost 30 000 children aged from 6 to 72 months living in an area of the Gangetic flood plain in Nepal has recently been reported. The study, which involved administration of gelatin capsules containing either 200 000 IU vitamin A or of placebo as a single dose every 4 months, was concluded prematurely when, at 12 months, 30% fewer deaths had been reported within the treated group (95% confidence interval 0.56-0.88) (10). Most significantly reduced were deaths ascribed to diarrhoea or dysentery, wasting malnutrition and measles. Unexpectedly, no decrease in deaths resulting from respiratory infections was recorded.

The results of this trial are of particular importance in two respects. They largely dispel earlier speculation that the benefits of replacement therapy in vitamin A deficient children may be dependent in some way on other unknown facilitating factors (11-13). They also confirm that, pending efforts to increase the dietary content of vitamin A, periodic administration of high-dose supplements offers a practicable interim expedient. It is estimated that in Nepal alone, where at least 2% of preschool children are xerophthalmic and many more are deficient in vitamin A (14), more than 15 000 lives could be saved each year. Throughout southern Asia as a whole, over a million lives may well be at issue every year (10).

References

1. WHO/UNICEF/IVACG Task Force. Vitamin A supplements. A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. Geneva: World Health Organization, 1988.
2. Sommer, A., Katz, J., Tarwatjo, I. Increased risk of respiratory disease and diarrhoea in children with preexisting mild vitamin A deficiency. *American Journal of Clinical Nutrition*, **40**: 1090-1095 (1984).
3. Bloem, M., Wedel, M., Egger, R. et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhoea in preschool and school children in north eastern Thailand. *American Journal of Epidemiology*, **131**: 332-339 (1990).
4. Barclay, A., Foster, A., Somme, A. Vitamin A supplements and mortality related to measles: a randomized clinical trial. *British Medical Journal*, **294**: 294-296 (1987).
5. Hussey, G., Klein, M. A randomized, controlled trial of vitamin A in children with severe measles. *New England Journal of Medicine*, **323**: 160-164 (1990).
6. Vijayaraghavan, K., Radhalah, G., Prakasam, B. et al. Effect of massive dose vitamin A on morbidity and mortality in Indian children. *Lancet*, **336**: 1342-1345 (1990).
7. Sommer, A., Tarwatjo, I., Djunaedi, E. et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. *Lancet*, **1**: 1169-1173 (1986).
8. Muhilal, D., Permeisih, D., Idjrsdinata, Y. et al. Vitamin A-fortified monosodium glutamate and health, growth and survival of children: a controlled field trial. *American Journal of Clinical Nutrition*, **48**: 1271-1276 (1988).
9. Rahmathullah, L., Underwood, B., Thulasiraj, R. et al. Reduced Mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine*, **323**: 929-935 (1990).
10. West, K., Pokhrel, R., Katz, J. et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet*, **338**: 67-71 (1991).
11. Reddy, V., Vijayaraghavan, K. Vitamin A and childhood mortality. *Lancet*, **337**: 232 (1991).
12. Sommer, A., West, K. Vitamin A and childhood mortality. *Lancet*, **337**: 925 (1991).
13. Thumham, D. Vitamin A and childhood mortality. *Lancet*, **337**: 232 (1991).
14. West, K. Vitamin A delivery in Nepal: building a natural strategy. *Proceedings of the XIII IVACG meeting, Kathmandu, Nepal*. The International Life Sciences Institute/Nutrition Foundation, Washington, D.C., 1990, pp. 11-18.