

Reports on Individual Drugs

Progress with rotavirus vaccines

In recent years, spectacular advances in immunology and biotechnology have provided the means to create new approaches to vaccine development. Techniques that for more than two centuries relied essentially on the inspired empiricism of Jenner have now been complemented by the new-found ability of molecular biologists to identify, isolate and replicate immunogenic foci in the structural proteins of cellular and subcellular pathogens and to create candidate vaccines by inserting them into suitable carriers or by coupling them with adjuvants.

Many effective products, none the less, are still manufactured by established traditional methods. Some, including live polio vaccine, measles, mumps, rubella, and the antituberculosis BCG vaccine, are naturally-occurring, attenuated strains of organisms that induce immunity in the host without invoking clinically significant disease. Others — notably influenza haemagglutinin and plasma-derived hepatitis B surface antigen — are subcellular components of pathogenic organisms that act in the same way. Yet others, such as killed polio and pertussis vaccines and diphtheria and tetanus toxoids, are either pathogens or products of pathogens that have been inactivated without destroying their immunogenic potential.

The developmental challenges which new vaccines still pose are well illustrated by ongoing efforts to develop an effective defence against human rotavirus, which is responsible worldwide for a substantial proportion of serious cases of diarrhoea in infants, both in developed and developing countries. In older children bacteria are responsible for most cases of infective diarrhoea, but since the discovery of the human rotavirus in the early 1970s (2, 3), it has become apparent that possibly as many as 30 per cent of the three million diarrhoeal deaths estimated to occur annually in children aged between 6 and 24 months could be averted if an effective vaccine were generally available (4).

Studies of rotaviruses isolated in many countries have resulted in the identification of four serotypes (5, 6). Of these, serotype-1 (subgroup 2) is most frequently implicated in epidemic outbreaks in developed countries, but all have been associated with clinical disease. The serum antibodies induced by these antigenic loci have been used as epidemiological markers of post-infection resistance (7). However, clinical immunity may also be determined by the development of mucosal anti-bodies in the gastrointestinal tract (8). Research has consequently been focused on the development of a live virus vaccine. Several approaches have been explored. Some have subsequently been punctuated by setback, but at least one vaccine now being tested clinically remains a possible candidate for commercial development.

Live attenuated human rotavirus

Some of the first studies were undertaken with a tissue-culture adapted mutant of a human serotype-1 virus developed in the United States National Institute of Allergy and Infectious Diseases. This retained its antigenicity and did not induce diarrhoeal illness in susceptible adult volunteers (9). However, mild elevation of serum transaminases in some subjects, and possible contamination of the product with simian viruses resulted in the foreclosure of the trials (10). More recently, naturally avirulent strains obtained from infants have engaged attention (11), although effort is now largely centred upon antigenically-related rotaviruses derived from calves and rhesus monkeys.

Bovine rotaviruses

Interest in animal rotaviruses was first aroused in 1975 by a demonstration that calves immunized *in utero* with a bovine rotavirus were resistant after birth to challenge with a serotype-1 strain of human rotavirus (12). Oral administration of this bovine virus, attenuated by passage in bovine kidney cells and produced in primary monkey kidney cells, was shown in an initial trial to be capable of inducing an important measure of resistance to rotavirus diarrhoea in infants and young children. Vaccination of Finnish children aged 8 to 11 months in a random-

ized study provided almost 90 per cent protection against severe rotavirus diarrhoea (13) and this advantage was maintained throughout a second epidemic season (14).

Similarly, encouraging results have been obtained in a second Finnish (15) study and in Peru (11). They were not matched, however, in trials in Rwanda (16), Gambia (17), or in a native American reservation in the USA (11). In these areas, a single dose of the vaccine conferred little or no protection possibly because of lower "take" rate rather than inherent resistance (18).

In the meantime, work had already begun at the Wistar Institute, Philadelphia on the development of an antigenically similar, but more highly immunogenic bovine rotavirus (WC3) (19). Thus far, the results continue to provide grounds for optimism. No serious rotavirus infections have been reported in samples of about 100 infants vaccinated respectively within the USA and in France, and the estimated protection rate for mild disease was in excess of 70 per cent in both studies (20, 21). Particularly impressive is the apparent capacity of the vaccine to confer protection against serotype-1 rotavirus even though neutralization tests provide no indication of an antigenic relationship. If trials currently planned or underway in Brazil, the Central African Republic, China, France, Israel and the USA indicate that the virus is both safe and protective against all serotypes and in both epidemic and endemic situations, WC3 will have satisfied the criteria required of a commercially-viable vaccine.

Simian rotaviruses

The rhesus rotavirus was selected within the US National Institute of Allergy and Infectious Diseases for three reasons (1). The major neutralization protein is closely related, if not identical, to that of the human rotavirus serotype-3 (5). It is readily grown in a rhesus monkey lung diploid cell strain developed as a potential cell substrate for vaccine production, and there is no evidence that it is a natural pathogen for man (1). Initial experience gained in the USA with a candidate vaccine in adults and older children indicated that it was both immunogenic and safe (1, 22). However, in infants and small children it has been associated with a significant incidence of fever and watery diarrhoea (23- 25). Used at lower dosage in a Venezuelan community, where serotype-3 rotavirus was predominant, it has conferred excellent protection without demonstrable adverse effect when administered to infants between one and ten

months old (26, 27). It does not appear to be active, however, against serotype-1 rotavirus (11, 19). In the event that a polyvalent vaccine is needed because candidates active against serotype-1 rotavirus are found to confer limited heterotypic protection, these results will have important significance.

Polyvalent vaccines

Candidate polyvalent vaccines are most simply prepared by co-infecting animal models with two strains of rotavirus and searching for genetically-promising reassortants. A breakthrough occurred when a modified rhesus monkey virus containing the human virus serotype-3 gene — which encodes the major neutralizing antigen — was generated in this way and subsequently isolated (28). Other reassortants with antigenic specificities for the other serotypes have since been obtained and combined to prepare a live, attenuated tetravalent vaccine that is already in clinical trial in the Peru and Venezuela (19). Preliminary studies indicate that it is acceptably safe, but further development has been interrupted by evidence that it is both less immunogenic and efficacious than its serotype-1 rotavirus component. Work is ongoing to explore whether this apparent interference between the various components can be overcome by modifying the existing preparation (19).

Further ahead lies the possibility, should need arise, of synthesizing specific polypeptide fragments of rotavirus DNA and cloning them in enteric bacteria or other vectors which could themselves be used as vaccines. The direction of any future research will, however, be determined primarily by the performance of those candidate vaccines already in clinical trial. If, in the event, the promise of the bovine WC3 vaccine is realized, it will provide a forceful reminder that traditional approaches to vaccine development still hold important potential.

References

1. Kapikian, A.Z., Midthun, K., Hoshino, Y. et al. Rhesus rotavirus: a candidate vaccine for prevention of human rotavirus disease. In: Lerner, R.A. et al., eds. *Vaccines 85*. Cold Spring Harbor Laboratory, New York, USA (1985), pp. 357-367.
2. Kapikian, A.Z., Wyatt, R.G., Dolin, T.S. et al. Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious nonbacterial gastroenteritis. *Journal of Virology*, **10**: 1075 (1972).

3. Bishop, R.F., Davidson, G.P., Holmes, I.H. et al. Virus particles in epithelial cells of duodenal mucosa from children with viral gastroenteritis. *Lancet*, 2: 1281 (1973).
4. De Zoysa, I., Feachem, R.G. Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization. *Bulletin of the World Health Organization*, 63: 569-583 (1985).
5. Hoshino, Y., Wyatt, R.G., Greenberg, H.B. et al. Serotypic similarity and diversity of rotaviruses of mammalian and avian origin as studied by plaque reduction neutralization. *Journal of Infectious Diseases*, 149: 694-702 (1984).
6. WHO Programme for Diarrhoeal Disease Control. Scientific Working Group on Viral Diarrhoeas. Nomenclature of human rotaviruses: designation of subgroups and serotypes. *Bulletin of the World Health Organization*, 62: 501-503 (1984).
7. Chiba, S., Nakata, S., Urasawa, T. et al. Protective effect of naturally-acquired homotypic and heterotypic rotavirus antibodies. *Lancet*, 2: 417-421 (1986).
8. Kapikian, A.Z., Wyatt, R.G., Greenberg, H.B. et al. Approaches to immunization of infants and young children against gastroenteritis due to rotavirus. *Reviews of Infectious Diseases*, 2: 459-469 (1980).
9. Kapikian, A.A., Wyatt, R.G., Levine, M.M. et al. Studies in volunteers with human rotaviruses. *Developments in Biological Standardization*, 53: 209 (1983).
10. Kapikian, A.Z., Hoshino, Y., Flores, J. et al. Alternative approaches to the development of a rotavirus vaccine. In: Holmgren, J. et al., ed. *Development of vaccines and drugs against diarrhoea*. 11th Nobel Conference, Stockholm (1986), pp. 192-214.
11. Black, R.E., Lanata, C.F. Development of rotavirus vaccines (in press).
12. Wyatt, R.G., Mebus, C.A., Yolken, R.H. et al. Rotaviral immunity in gnotobiotic calves: heterologous resistance to human virus induced by bovine virus. *Science*, 203: 548-550 (1975).
13. Vesikari, T., Isolauri, E., D'Hondt, E. et al. Protection of infants against rotavirus diarrhoea by RIT 4237 attenuated bovine rotavirus strain vaccine. *Lancet*, 1: 977-981 (1984).
14. Vesikari, T., Isolauri, E., André, F.E. et al. Protection of infants against human rotavirus diarrhea by the RIT4237 live attenuated bovine rotavirus vaccine. In: Lerner, R.A. et al., ed. *Vaccines 85*. Cold Spring Harbor Laboratory, New York, USA (1985). pp. 369-372.
15. Vesikari, T., Isolauri, E., Delen, A. et al. Clinical efficacy of the RIT 4237 live attenuated bovine rotavirus vaccine in infants vaccinated before a rotavirus epidemic. *Journal of Paediatrics*, 107: 189-194 (1985).
16. De Mol, P., Zissis, G., Butzler, J.P. et al. Failure of live attenuated oral rotavirus vaccine. *Lancet*, 2: 108 (1986).
17. Hanlon, P., Marsh, V., Shenton, F. et al. Trial of an attenuated bovine rotavirus vaccine (RIT 4237) in Gambian infants. *Lancet*, 1: 1342-1345 (1987).
18. Lanata, C.F., Black, R.F., del Aguila, R. et al. Protection of Peruvian children against rotavirus diarrhoea of specified serotypes by the RIT 4237 attenuated bovine rotavirus vaccine. *Journal of Infectious Diseases*, (in press).
19. Clark, H.F., Furukawa, T., Bell, L.M. et al. Immune response of infants and children to low-passage bovine rotavirus (strain WC3). *American Journal of Diseases of Children*, 140: 350-356 (1986).
20. Clark, H.F., Borian, F.E., Bell, L.M. et al. Protective effect of WC3 vaccine against rotavirus diarrhea in infants during a predominantly serotype-1 rotavirus season. *Journal of Infectious Diseases*, 158: 570-587 (1988).
21. Third Rotavirus Vaccine Workshop, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, 8-9 September, 1988.
22. Christy, C., Madore, P., Treanor, J.J. et al. Safety and immunogenicity of live attenuated rhesus-monkey rotavirus vaccine. *Journal of Infectious Diseases*, 154: 1045-1047 (1986).
23. Anderson, E.L., Belshe, R.B., Bartram, J. et al. Evaluation of rhesus-rotavirus vaccine (MMU 18006) in infants and young children. *Journal of Infectious Diseases*, 153: 823-831 (1986).
24. Losonsky, G.A., Rennels, M.B., Kapikian, A.Z. Safety, infectivity, transmissibility and immunogenicity of rhesus rotavirus vaccine (MMU 18006) in infants. *Pediatric Infectious Diseases*, 5: 25-29 (1986).
25. Vesikari, T., Kapikian, A.Z., Delem, A. et al. A comparative trial of rhesus-monkey (RRV-1) and bovine (RIT 4237) oral rotavirus vaccines in young children. *Journal of Infectious Diseases*, 153: 832-839 (1986).
26. Perez-Schael, I., Gonzalez, M., Daoud, N. et al. Reactogenicity and antigenicity of the rhesus rotavirus vaccine in Venezuelan children. *Journal of Infectious Disease*, 155: 334-338 (1987).
27. Flores, J., Gonzalez, M., Perez, M. et al. Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants. *Lancet*, 1: 882-884 (1987).
28. Midthun, K., Greenberg, H.B., Kapikian, A.Z. et al. Reassortant rotaviruses as potential live rotavirus candidates. *Journal of Virology*, 53: 949-954 (1985).

Interferon alfa for Kaposi's sarcoma

United States of America — Two slightly different molecular versions of a high dosage form of injectable interferon alfa (Hoffman-La Roche and Schering) have been approved by the Food and Drug Administration for the treatment of Kaposi's sarcoma. Best response rates in AIDS patients have been obtained in individuals who were otherwise asymptomatic, with a baseline T4 lymphocyte count greater than 200/mm³ and no history of prior opportunistic infection. Plans are now in hand to conduct a trial in which the effect of a combination of interferon alfa plus zidovudine will be compared with interferon alfa alone.

Previously, Kaposi's sarcoma was generally treated with chemotherapy and radiation. However, chemotherapy tends to increase the risk of severe opportunistic infections, while radiation therapy could only be used for the treatment of localized tumours.

Lower dose formulations of interferon alfa remain available for treating hairy cell leukaemia and genital warts.

Reference: *FDA Drug Bulletin*, 19: Number 1 (1989).

Does clioquinol prevent bacterial diarrhoea?

Clioquinol has been used for over 50 years to treat and prevent diarrhoeal disease. Some evidence exists to show that it is effective in eradicating amoebic cysts (1-3), but its value in bacterial infections has never been firmly established. It remains a popular household remedy in many developing countries to treat episodes of acute diarrhoea but, as a result of its association with an epidemic of subacute myelo-optic neuropathy in Japan in the early 1970s (4), it has long been withdrawn in many countries.

Because of the unpredictable pattern of incidence, varied etiology and self-limiting nature of non-specific diarrhoea, evidence to confirm or refute the claim that clioquinol is of value in this condition is not readily generated. Some studies have suggested it offers protection against travellers' diarrhoea and

shigellosis, while others have shown no advantage over placebo. In these circumstances, the recent development of an animal model intended to demonstrate intraluminal antibacterial activity is of particular interest (5). Colonization of rabbit intestine by *Vibrio cholerae* and *Escherichia coli* was inhibited, as expected, by tetracycline while the effect of clioquinol was minimal. The discriminatory potential of the model clearly cannot be established on the basis of these data alone, but the results inevitably cast further doubt on whether clioquinol offers any tangible benefit in the treatment and prevention of acute diarrhoea.

References

1. David, N. A., Johnstone, H. G., Reed, A. C. et al. The treatment of amoebiasis with iodochlorhydroxyquinolone (Vioform NNR). *Journal of the American Medical Association*, 100: 1658-1661 (1933).
2. Gholz, L. M., Arons, W. L. Prophylaxis and therapy of amoebiasis and shigellosis with iodochlorhydroxyquinolone. *Journal of Tropical Medicine and Hygiene*, 13: 396-401 (1964).
3. Powell, S. J., Wilmot, A. J., Elsdon-Dew, R. Potentiating effect of quinolines on the action of tetracycline in amoebic dysentery. *Lancet*, 1: 76-77 (1960).
4. Nakae, K., Yamamoto, S. I., Igata, A. Subacute myelo-optic-neuropathy (SMON) in Japan. *Lancet*, 2: 510-512 (1971).
5. Sack, D. A., Cray, W. C., Alam, K. Comparison of prophylactic tetracycline and clioquinol in a rabbit model of intestinal infection with *Vibrio cholerae* and *Escherichia coli*. *Chemotherapy*, 33: 428-436 (1987).

Vaccination against Japanese encephalitis

The Japanese encephalitis virus, which is related to the flaviviruses responsible for yellow fever and dengue, is transmitted to man from a natural reservoir of birds and mammals by a species of culex mosquito. It occurs in annual epidemics in many of the major rice-growing areas of Asia and is the most highly prevalent form of encephalitis in the world. Annual attack rates in excess of 10 to 20 per 100 000 are recorded in highly endemic areas and many of the infected patients either die or are left permanently handicapped.

A highly purified formalin-inactivated vaccine containing the Nakayama-NIH strain of the virus has been administered routinely to Japanese children since 1965. Controlled studies of its efficacy have recently been greatly facilitated by the development of an IgM enzyme-linked immunosorbent assay (ELISA) which can be used to test either cerebrospinal fluid or serum for antibody. This development has been used in a joint study undertaken in Northern Thailand by the United States Armed Forces Research Institute of Medical Sciences and the Research Institute for Microbiological Diseases of the University of Osaka, Japan, to test the protective effect of both the Nakayama-NIH strain and a bivalent vaccine additionally containing a Chinese (Beijing-1) strain.

In all, a total of 65 224 children aged between 1 and 14 years living in an area comprising 458 villages were enrolled in the study. Each subject was randomly allocated either to the monovalent preparation, the bivalent preparation, or to tetanus toxoid. The cumulative attack rate for the disease over the subsequent year was 51 per 100 000 in the comparator group and 5 per 100 000 in each of the vaccinated groups. On this basis, both vaccines were estimated to confer a degree of protection of between 70 to 97 per cent (95 per cent confidence interval). Fewer cases of unexplained illnesses involving the central nervous system were recorded among the vaccinated children than within the comparator group and short-term adverse effects were described as minimal. An associated reduction in the attack rate for dengue fever, which was also noted during the first few months after vaccination, did not attain statistical significance, but some reduction was also claimed in the severity of cases within the vaccinated groups. Evidence of safety was similarly encouraging.

Notwithstanding the apparent efficacy and safety of the vaccine, its relatively high cost and the need for rigorous determination of health priorities in the most highly endemic countries seem destined, at present, to preclude its general availability where it is most needed. None the less, the outcome of this trial creates a commitment for further study aimed at demonstrating how the vaccine might be most effectively incorporated into existing immunization schedules.

Reference: Hoke, C. H., Nisalak, A., Sangawhipa, N. Protection against Japanese encephalitis by inactivated vaccines. *New England Journal of Medicine*, 319: 608-643 (1988).

Human insulins: an update

United Kingdom — A recent review carried in the *Drug and Therapeutics Bulletin* acknowledges the production of human insulin, whether by genetic engineering or modification of pork insulin, to be a formidable technical achievement. It questions, however, whether the claims now made for human insulin as being "identical to the body's own insulin and therefore the logical choice" and "outstandingly pure and less immunogenic" are justified in the light of their proven clinical performance.

The *Bulletin* concedes that an absolute need for transfer from animal to human insulin arises in very rare cases of allergy. However, in no other circumstance does it consider that transfer will solve problems inherent in the management of insulin-dependent diabetes mellitus. It emphasizes, moreover, that human and animal insulins cannot be regarded as essentially interchangeable. Human insulins are absorbed slightly faster after subcutaneous injection than the corresponding pork formulations, and human insulin zinc suspension (crystalline) is absorbed much faster than bovine ultralente. Less well-established, but of undoubted concern, are claims that human insulins alter subjective awareness of hypoglycaemia so that adrenergic symptoms, such as sweating and palpitations, are less prominent and neurological symptoms supervene without the usual warning.

Many brands of animal insulin have now been withdrawn, yet no adequate replacement has yet been offered for the very-long-acting beef lente and ultralente preparations. These, in the view of the *Bulletin*, will be missed — particularly in the management of patients requiring a background of long-acting insulin supplemented by soluble insulin and of elderly patients in whom a single daily injection is convenient. In general, it advises doctors that patients who are adequately controlled on animal insulins should remain on them. If a change to a human preparation is indicated for any reason the patient should always be advised that fine retuning of the dose may be necessary and that warning symptoms of hypoglycaemia may change in character.

Reference: Human insulins: an update. *Drug and Therapeutics Bulletin*, 27: Number 6 (1989).

Adjuvant treatment of early breast cancer

The *New England Journal of Medicine* has recently published an overview of 68 randomized trials of post-surgical tamoxifen or cytotoxic therapy in early breast cancer that were started before 1985 (1). These involved a total of some 30 000 women of whom more than 8 000 have subsequently died. The results have established that both interventions tend to reduce five-year mortality. The effect of tamoxifen — usually administered in doses of at least 20 mg daily for two years or more — was most marked among women aged over 50, in whom mortality was reduced by some 20 per cent. The beneficial effects of chemotherapy, in contrast, were more evident in younger women in whom overall mortality was reduced by one quarter. Combination chemotherapy was more effective than single drug therapy, but treatment for 8 to 24 months offered no clear advantage over the same regimen administered for 4 to 6 months. Clear survival benefit from chemotherapy was not evident in women aged over 50, regardless of the type of regimen employed. Tamoxifen appeared to be equally effective among older women when administered alone or in combination with chemotherapy, while in younger women, the possibility of a negative interaction between the two types of therapy could not be discounted.

Thus far, the greatest absolute reductions in mortality have been recorded among patients with a relatively poor prognosis. The authors accept, however, that additional years of follow-up may appreciably alter this interpretation and they emphasize that, notwithstanding the size of the present overview, more information is required both on different subsets of patients, and on more prolonged hormonal therapy and more intensive chemotherapy. Of particular note is the limited amount of information provided by the survey on women without nodal involvement, and the lack of statistical evidence that therapy is associated with reduction of mortality in this important group.

More recently, the *New England Journal of Medicine* has returned to this debate by publishing simultaneously four reports of studies of different adjuvant regimens in women with node-negative breast cancer:

- a single perioperative course of cyclophosphamide, methotrexate, fluorouracil and leucovorin.
- 12 postoperative courses of sequentially administered methotrexate and fluorouracil followed by leucovorin.
- six courses of cyclophosphamide, methotrexate, fluorouracil and prednisone.
- five years' treatment with the antiestrogen, tamoxifen.

Each group was observed for either three or four years post-operatively, and in each case treatment was evaluated through comparisons with randomly selected groups of women who received surgery alone. The disease-free survival rate of patients in the control groups ranged from 69 to 77 per cent. In each case, treatment was estimated to confer benefit of 6 to 15 percentage points. In no case, however, was any definite improvement in overall survival demonstrated. Moreover, the most effective treatment — regimen 3 — induced severe bone marrow impairment in one third of the patients and contributed to at least one death.

These results appear even more persuasive if they are expressed in terms of relative risks and odds ratios. In many other situations they would provide an uncontested basis for instituting therapeutic policy. In this instance, however, the editor offers two contrasting commentaries on whether adjuvant therapy now has a place in the routine management of early breast cancer (2, 3). An appealing argument favouring nonselective treatment is that in any situation in which chemotherapy is known to be effective, it can reasonably be expected to work best when the tumour burden is low. Conversely, it can be argued, given the high overall expectation of survival among these patients, those with the best prognosis — as identified, for instance, by tumours smaller than 2 cm diameter or diploid tumours with few cells in S phase — have least to gain from chemotherapy, while they share equitably the risk of acute toxic effects and the unevaluated hazards of delayed toxicity.

Also inevitably weighing in the balance is the consideration of cost. Calculations based on one of the selected regimens indicate that, on average, one patient would gain a disease-free survival advantage (not necessarily a cure) for every US\$ 67 000 spent on routine adjuvant treatment. Since breast cancer is a common condition, the practicability of such an approach — particularly in the absence of a proven survival benefit — must be open to question even within the most favoured economies. If, in time, a basis can be provided for selective and more cost-

effective treatment, through more precise definition of those women at greatest risk of recurrence, the feasibility of routine adjuvant therapy in these patients could be greatly enhanced. In the first instance, however, the need remains to establish the extent to which the treatments offered in trials already undertaken influence long-term survival.

References

1. Early Breast Cancer Trialists Collaborative Group. Effects of adjuvant tamoxifen and cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28 896 women. *New England Journal of Medicine*, **319**: 1681-1693 (1988).
2. McGuire, W. L. Adjuvant therapy of node-negative breast cancer. *New England Journal of Medicine*, **320**: 525-527 (1989).
3. DeVita, V. T. Breast cancer therapy: exercising all our options. *New England Journal of Medicine*, **320**: 527-529 (1989).

Estrogens and endometrial cancer

Sweden — Several case-control studies have indicated that prolonged treatment of menopausal problems with potent estrogenic drugs is associated, when they are administered alone, with an increased risk of endometrial cancer (1, 2). The addition of progestogens for at least 10 days of each treatment cycle seems to protect against endometrial hyperplasia (3), and a combined regimen is now commonly used to treat women who have not had their uterus removed.

Epidemiological demonstration of such protection has been awaited and this is now tentatively provided by preliminary data from a prospective cohort follow-up study undertaken in Sweden (4). Information on more than 23 000 women aged over 35 who had been prescribed estrogens for purposes other than contraception during a three year period between 1977 and 1980 were identified from pharmacy records, and those who subsequently developed endometrial neoplasia were detected from a regional cancer registry. During the period of observation 74 cases of carcinoma and 33 cases of premalignancy were reported within the cohort.

After appropriate adjustments had been made to exclude non-compliant patients and those who had undergone hysterectomy, it was estimated that the

risk of endometrial carcinoma was raised two to threefold among women who had taken any estrogen compound without concomitant progestogen for more than six years. No increase in risk was evident among women who had also taken progestogens throughout the period of treatment, and the added risk tended to decrease — although it was never entirely eliminated — among women who had been transferred at some stage from estrogen to estrogen/progestogen regimens. The authors emphasize, however, that further follow-up of the cohort is necessary, both to analyse the risk with increased statistical power and to determine whether it is entirely eliminated or merely delayed by use of progestogens.

References

1. Cramer, D. W., Knapp, R. C. Review of epidemiologic studies of endometrial cancer and exogenous estrogen. *Obstetrics and Gynecology*, **54**: 521-526 (1979).
2. Zeil, K. Estrogen's role in endometrial cancer. *Obstetrics and Gynecology*, **58**: 509-515 (1982).
3. Whitehead, M.I., Townsend, P.T., Pryse-Davies J. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New England Journal of Medicine*, **305**: 1599-1605 (1981).
4. Persson, I., Adami, H.-O., Bergkvist, L. Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *British Medical Journal*, **298**: 147-151 (1989).

Oral contraceptives and genital tract malignancies

United Kingdom — A further interim report on the Royal College of Practitioners' Oral Contraception Study has recently been published in the *Lancet* (1). It examines the incidence of reported cases of malignancies of the genital tract in the 47 000 women who were originally included in this prospective cohort study in 1968.

The data are presented to demonstrate relative excesses and deficits in the apparent incidence of specific malignancies between groups of women who have or who have not at any time taken oral contraceptive preparations. They confirm earlier independent findings that previous use of oral contraceptives reduces subsequent risk of cancer of the ovary and the body of the uterus (deficits of 4

and 5, respectively, per 100 000 women-years). However, this advantage is essentially offset by an increased incidence of invasive cervical carcinoma (excess 8 per 100 000 years), and it is more than counterbalanced when carcinoma-in-situ is additionally taken into consideration (excess 41 per 100 000 years).

The magnitude of this positive association with cervical carcinoma is obviously disquieting. Suggestions have been made that the design of the study has resulted in over-estimation of the risk (2), and the debate as to whether oral contraceptives play a causal or secondary role in its etiology continues unresolved. However, the clinical implications of the findings remain the same regardless of their determinants. Invasive cervical cancer is potentially preventable by effective screening and particular attention should be given to its early detection in women who have used oral contraceptives.

References

1. Beral, V., Hannaford, P., Kay, C. Oral contraceptive use and malignancies of the genital tract. *Lancet*, 2: 1331-1335 (1988).
2. Narod, S. A., Miller, A. B. Oral contraception and genital-tract malignancy. *Lancet*, 1: 377 (1989).

Almitrine: peripheral polyneuropathy

Netherlands — Some disquieting results have been reported from a double-blind, placebo-controlled study of the respiratory stimulant almitrine in patients with chronic obstructive airways disease. Ten patients received almitrine 50 mg twice daily and, in non-responsive patients, this was increased after three months to a maximum of 200 mg daily. Four patients had to withdraw from the trial prematurely when they developed signs of peripheral polyneuropathy. These were still apparent in one patient three years later. The authors consider that this neurotoxic effect imposes an important constraint on the use of the drug, particularly since its development is not closely correlated with plasma levels.

Reference: Wouters, E.F.M., Greve, L.H., Steenhuis, E.S. et al. Almitrine and peripheral neuropathy. *Lancet*, 2: 336 (1988).

Fast tests for HIV-1 antibodies

United States of America — The Food and Drug Administration has licensed a latex agglutination test for the detection of human antibody to HIV-1 that can be performed and read within 5 minutes. It is not intended to replace the enzyme-linked immunosorbent assay (ELISA), which remains preferred for routine use in blood banks and clinical laboratories, but it is expected to be particularly useful as a screening test in remote areas where the ELISA cannot be properly processed.

Because the test occasionally generates false-positive results it is not well adapted to screen large numbers of samples and positive results should always be confirmed by a more specific test such as the Western blot.

The antigen used in the new test is a genetically engineered protein containing sequences related to the HIV-1 virus envelope and expressed in *Escherichia coli* bacteria. It is produced more safely than the antigen of the ELISA which is obtained from live HIV-1 virus grown in cell culture.

Reference: *FDA Drug Bulletin*, 19: Number 1 (1989).

Ganciclovir and cytomegalovirus retinitis

United States of America — The Food and Drug Administration has made special arrangements to release intra-venous ganciclovir for the treatment of AIDS patients with immediately sight-threatening cytomegalovirus retinitis. To qualify for treatment, patients must discontinue taking zidovudine because both drugs are toxic to white cell blood precursors. Between 20 to 30 per cent of patients on ganciclovir have had to discontinue treatment, at least temporarily, because of neutropenia. With the exception of aerosolized pentamidine, the Food and Drug Administration considers that all other drugs — including antimetabolites, alkylating agents, interferon, cytokines, systemic aciclovir and other nucleoside analogues — should be withdrawn during therapy because of the potential for additive toxicity.

Reference: *FDA Drug Bulletin*, 19: Number 1 (1989).