

# Reports on Individual Drugs

## Iron deficiency and developmental retardation

Over the past 15 years, many studies undertaken in a variety of settings in both developed and developing countries have demonstrated a correlation between iron deficiency in infancy and subsequent retardation of mental and motor development (1-5). Some studies offer circumstantial evidence that correction of the deficiency rapidly improves performance, but only recently has this expectation been proven within the context of a randomized, double-blind trial (6).

Fifty infants aged between 12 and 18 months with iron-deficiency anaemia and who were otherwise normal (haemoglobin 105-180 g/L) were randomly assigned to receive either ferrous sulphate, 3 mg elemental iron/kg, or a matching placebo syrup for 4 months. Two other groups of infants who were either iron-sufficient or who had non-anaemic iron-deficiency (haemoglobin >120 g/L; transferrin saturation <10%; serum ferritin <12 µg/L) were also randomized to the same treatments. All the infants were tested with the Bayley scales of mental and motor development both one day before and on completion of the treatment. Following the intervention, developmental delays were reversed selectively among those iron-deficient anaemic infants who had received iron. Neither the iron supplement nor placebo had demonstrable effect on the scores of the non-anaemic infants.

It is encouraging that, within the context of this trial, iron-deficiency anaemia was not associated with irreversible developmental delays. The extent to which this outcome is applicable to older children or to those with more severe degrees of anaemia has yet to be established. It has been claimed, none the less, that within communities at risk of iron deficiency, mental development scores do not predict differences in intellectual function in later childhood (7), whereas the level of motor maturation at 15 months predicts cognitive test performance at 18 years of age (8).

The reasonable generalization to draw from the facts now available is that iron deficits in young children should be promptly rectified whenever practicable. Iron deficiency is readily diagnosed and

highly prevalent in deprived communities (9). As yet, however, national screening programmes are the exception rather than the rule even in developed countries. As an alternative, fortification of weaning foods with iron has been proposed as a prophylactic measure. Administration of iron supplements to children who do not require them is sometimes viewed with reticence. It is notable that, within the context and timespan of this trial no ill effects resulted from unnecessary supplementation (10).

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## Vitamin A deficiency and abnormal T-cell subsets

Vitamin A deficiency in children, which remains a highly prevalent consequence of malnutrition in many developing countries, has long been recognized as the cause of xerophthalmia. More recently, even mild deficiency has been associated in various studies with increased mortality (1-3) that results from increased vulnerability to intercurrent infections, notably measles (4, 5), diarrhoea and respiratory disease (6, 7).

Not all published studies have reported positive results (8-10) and, because the observations have been highly empirical, the inconsistency of the findings has remained essentially unexplained. Indeed, little attention has been given to the mechanisms by which vitamin A might exert these effects, although it has been recognized that deficiency is likely to be associated with impaired immune mechanisms (11, 12). Thus children deficient in vitamin A have been shown to have decreased IgG responses to tetanus toxoid (13); selective loss of CD4 cells from lymph nodes (14); and atrophy of the lymph nodes, thymus and spleen (15).

This hypothesis of impaired immune responsiveness has now been supported by demonstration of a cell-mediated immune defect in children marginally deficient in vitamin A (16). It is characterized by lowered ratios of helper (CD4) to suppressor (CD8) lymphocytes, and lower proportions of the naive subset of helper cells (in comparison with the memory phenotypes). Changes in these subsets have previously been described in several chronic infectious and parasitic diseases, including HIV infection, tuberculosis, leprosy, visceral leishmaniasis and onchocerciasis.

The practical importance of these findings is that they may lead to the identification of more sensitive and functionally significant indicators of immune competence in mild vitamin A deficiency (17). Moreover, a study of the time course of these changes could provide an indication of optimum dosage schedules and, in particular, the relative efficacy of interval supplementation compared with dietary supplementation through fortification of staple foodstuffs.

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### Ivermectin: a protective effect against onchocercal optic neuropathy?

Ivermectin, a semisynthetic macrocyclic lactone, has now been extensively used for more than 5 years, largely in West Africa, to suppress the progression of onchocerciasis (1). In a single oral dose of 150 µg/kg, it rapidly depresses the dermal microfilarial density to a low level which is maintained for more than 12 months and which is accompanied by a slow clearing of the microfilariae from the anterior chamber of the eye (2-4) and a diminution of anterior segment eye lesions, especially punctate corneal opacities and iridocyclitis (5, 6).

Histological studies of female worms suggest that this effect results, at least in part, from impairment of the normal intrauterine development of the microfilariae and inhibition of their release from the uterus (7, 8). Longer-term studies undertaken over a period of 3 years within a community of 14 000 workers and their families living on a rubber plantation in Liberia, have shown that this effect may be sufficient, given regular annual distribution of ivermectin, to substantially reduce the transmission of infection by the blackfly vectors (9).

Because the therapeutic effect of ivermectin is prolonged, and specifically because the microfilaricidal action is not abrupt, treatment with ivermectin apparently does not induce or aggravate the optic neuropathy sometimes associated with diethylcarbamazine (10, 11). Indeed, evidence recently reported (12) indicates — in contradistinction to earlier results from smaller trials (5, 6, 13) — that annual ivermectin therapy maintained over three consecutive years significantly reduces the incidence of the main potentially-blinding lesions of onchocerciasis — sclerosing keratitis, chorioretinitis and optic nerve disease.

This most recent study was conducted in the savannah of northern Nigeria, within 34 communities mesoendemic for onchocerciasis. More than 300 to 500 villagers aged 15 years or more were randomly assigned to an annual dose of ivermectin (weight-adjusted to provide a dose of some 100-200 µg/kg) or placebo. Ophthalmic examinations were performed on entry, after 2 years and after 3 years. A skin snip was also taken during the first examination to provide an estimate of the microfilarial load. In all, 3522 individuals were re-examined at least once, and 2588 were examined on all 3 occasions. Outcome was measured by monitoring for changes in visual function and increasing pallor of the optic disc.

Deterioration of the appearance of the optic disc was considered to have occurred in 116 patients during the course of the trial. Of these 45 patients had taken ivermectin and 71 placebo. The incidence of changes was much higher among subjects recorded as having a pale disk on admission to the study, and among those who had previously been treated with diethylcarbamazine. In neither of these groups was ivermectin demonstrated to offer protection. Nor was any effect evident among patients with microfilarial loads in the skin of less than 10 microfilariae/mg. However, among the greater number of subjects with no initial evidence of ophthalmic impairment and microfilarial loads greater than 10mf/mg, the incidence of disc deterioration was roughly halved by ivermectin. Indeed, it is possible that the true reduction may be substantially higher.

This study provides the most direct and conclusive evidence yet obtained that treatment with ivermectin may, in the longer term, substantially decrease the risk of onchocercal blindness. It is impossible to be certain whether or not the results obtained in the savannah might also be obtained in the rain forests of the Volta river basin. DNA probes have shown differences to exist in both the vectors and the parasites prevalent in the two environments (14). There is reason for optimism (15) since: blindness more frequently results from posterior segment involvement (chorioretinitis and optic nerve disease) in the forests (16), and from anterior segment disease (sclerosing keratitis and uveitis) in the savannah (17).

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## Artesunate/mefloquine in acute uncomplicated falciparum malaria

The attack rate for falciparum malaria along Thailand's northern borders is among the highest in the world. About 300 000 cases are now reported annually within the country, of which some 2000 to 4000 are fatal (1). The situation is the more alarming in the face of increasing multidrug resistance. The efficacy of a combination of mefloquine, sulfadoxine, and pyrimethamine used within Thailand in the late 1980s (2) — but which is no longer recommended — had decreased from an estimated 98% to about 70% by 1990 (3-5). A similar pattern of failure has been reported among patients treated with mefloquine alone at higher dosage (18-25 mg/kg) (5), and with halofantrine (6).

In Thailand in 1991, a trial of an oral formulation of artesunate, a derivative of artemisinin, administered in a total dose of 600 mg over 5 days produced a cure rate of 90% (7). This is comparable to success rates reported elsewhere with artemisinin and its derivatives — largely in southeast Asia, and particularly in China, where the antimalarial properties of artemisinin were discovered (8-17). It is generally agreed that these agents are highly effective in clearing parasitaemia, but rates of recrudescence ranging up to 50% were reported in some of the earliest trials.

Recrudescence is not simply a manifestation of treatment failure, it also favours the development of drug-resistant strains of *Plasmodium falciparum*. There is consequently a strong rationale to use artemisinin derivatives together with other anti-malarial agents — either concomitantly or sequentially — in the oral management of uncomplicated malaria. Having regard to laboratory evidence of synergism between these derivatives and mefloquine in their antimalarial effects (18, 19) a random-

ized trial has recently been conducted in Thailand to compare the efficacy of artesunate (600 mg over 5 days) and mefloquine (750 mg followed by 500 mg 6 hours later) both alone and in sequence in the treatment of uncomplicated falciparum malaria (19).

In all, about 40 patients with acute, uncomplicated falciparum malaria were allocated to each of these 3 treatment groups. Cure rates of between 80% and 90% were obtained with each of the single drug regimens and, most impressively, all the patients who received the combination therapy responded satisfactorily and no recrudescence occurred within this group during 28 days of follow-up. Fever abated and parasites were cleared more rapidly among patients who received artesunate and, although the incidence of nausea and vomiting was slightly higher among the patients who received both drugs, the difference was not significant.

The efficacy of this combination obviously merits investigation within considerably larger samples of patients. If recrudescence is confirmed to be a rare event, an important step may well have been achieved in frustrating the emergence of strains of *P. falciparum* resistant to a vital series of anti-malarial compounds.

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### ***Haemophilus influenzae* vaccines: a third generation in prospect?**

It has been claimed that ten years ago *Haemophilus influenzae* type b (Hib) infections caused as much permanent disability and death among infants and young children in the United States as the poliomyelitis epidemics of the 1950s (1). As many as 1 in 200-300 children developed invasive Hib disease before their fifth birthday (2). Most of the serious consequences of infection resulted from bacterial meningitis, largely in children aged less than 2 years (3, 4). The overall mortality rate for invasive disease among children under 5 years ranged from 3 to 6% and, among the 60% who presented with meningitis, the incidence of permanent neurological deficit among survivors was 20 to 30% (4-6).

The first vaccines to offer protection against these infections contained Hib capsular polysaccharide. An early trial conducted in Finland in the 1970s showed that one of these products was highly effective in a single dose in children aged 18 months to 6 years, but of virtually no value in the younger children who are most vulnerable to infection (7, 8). This was followed by a series of postmarketing studies undertaken in the USA which generated inconsistent — and often unsatisfactory — results, even when administered to children in the older age group (9).

These disappointing results stimulated the development of a second generation of vaccines in which the polysaccharide antigen is conjugated to protein complexes derived from meningococci or the diphtheria bacillus (9). These were initially licensed in the United States for older children early in 1988. Only late in 1990, on the basis of successful clinical trials in infants (10, 11), were they licensed for use in all children over 2 months of age.

Conjugation of the polysaccharide antigen enhances its immunogenicity in infants and induces

“immunological memory” so that an anamnestic — or secondary — response occurs on subsequent antigenic challenge (12, 13). Within the past few months no less than five independent reports have been published that describe an impressive decline, ranging from 70 to 90%, in the incidence of meningitis and other invasive diseases attributed to *H. influenzae* among children in the United States since the introduction of these vaccines (14-18). Similar findings have been reported from Finland (19). Indeed, expectation has been raised that *H. influenzae* meningitis may be eliminated in areas where high vaccination coverage has been achieved (19, 20).

At the same time, cautious reminders have been offered that changes in the incidence of a disease over time cannot alone establish the efficacy of a vaccine (21). It has been pointed out that, not only was a decline apparent in the incidence of invasive haemophilus infections among children under 18 months of age in the United States within the period 1985-1988 before the conjugated vaccines became generally available, but that the subsequent accelerated decline was already apparent before the conjugated vaccine was administered to the more vulnerable younger children late in 1990.

However, it is premature to suggest that the eclipse of invasive haemophilus disease might have been no more than coincidental with the introduction of conjugated vaccine. It is possible that reduced pharyngeal carriage of Hib in the older vaccinated children throughout 1988-1990 may have reduced exposure among younger unprotected children (21-24). Such speculation would stand on firmer ground if more detailed data were available about the coverage of vaccination year by year within the populations that have been studied, and if more were known on trends in the incidence of invasive haemophilus infections over the past decade in countries where no vaccine has yet entered into widespread use.

On the assumption that vaccination has provided an important degree of protection, there is need for sustained epidemiological examination of its effects. There is need to know at the earliest opportunity how long any protective degree of immunity will persist after vaccination, and of the possible susceptibility to clinical infection later in life of a generation of vaccinated individuals, unprotected by antibodies induced by pharyngeal colonization (21, 25).

Surveillance also holds importance in another context. The available vaccines offer protection

against type b capsular forms of *H. influenzae* but non-capsular forms and other serotypes of the organism are also potential pathogens. Whereas these are only rarely associated with meningitis, they are a major cause of acute otitis media, sinusitis, and lower respiratory infections (20, 26). The acutely infected respiratory tract is particularly vulnerable to secondary invasion by *H. influenzae* (27), and in some developing countries it has been estimated that this organism is responsible for 30 to 40% of all lower respiratory tract infections, including many cases of lobar pneumonia (28-30).

Some years ago a preliminary study indicated that oral immunization with killed *H. influenzae* might well provide useful protection against exacerbations of acute bronchitis in patients with chronic obstructive lung disease (31). The potential of developing vaccines against other types of *H. influenzae* is clearly worthy of further investigation. The immediate challenge, however, is to consider how a vaccine that offers protection against more than one in three cases of childhood bacterial meningitis (19) can be made extensively available where it is most needed.

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## Pertussis: a rationale for adult vaccination?

Pertussis is widely but mistakenly regarded as a disease that occurs essentially in children (1-9). In the United States, between 1980 and 1989, approximately 12% of reported cases occurred in individuals older than 15 years (10), and the results of two localized surveys — one undertaken in the United States and the other in Australia — suggest that about one-quarter of all adult patients with chronic cough now have serological evidence of recent *Bordetella pertussis* infection (9, 11).

Ironically, it is the extent and success of childhood vaccination programmes that has resulted in this transformation (1). In the prevaccine era, virtually all adults had long-standing immunity as a result of infection during childhood. It is estimated that as many as 50 million adults in the United States are now susceptible to pertussis, and that atypical disease in adults now provides the primary reservoir of infection (12). Indeed, some US investigators even suggest that, where vaccination coverage is high, pertussis is already essentially a disease of adults (5).

Because of the history of litigation associated with pertussis vaccines, no trials of whole-cell pertussis vaccines have been undertaken in adults, but several acellular pertussis vaccines have been shown to be both immunogenic and well tolerated in adult populations in recent trials (13-17). None the less, analysis of attack rates during outbreaks of pertussis (18, 19) and measurement of post-immunization levels of pertussis antibodies (13) has provided evidence of waning immunity within 2 to 3 years.

It is too early to judge if, or when, adults will require booster injections, since no correlation has yet been made between the levels of different types of antibodies and protection against clinical disease (13). This is an important point to resolve. There is no doubt that adults without adequate immunity are liable to carry and spread the organism, and *B. pertussis* continues to circulate even in highly immunized populations (20).

As yet, the mechanism of immunity induced by these vaccines remains uncertain. Several observations, including data on T-cell proliferation (21) and increased susceptibility of patients with HIV infection (22), suggest that cell-mediated immunity

is important. Immunization also stimulates production of humoral antibody, but it does not stimulate local secretory antibody needed to prevent attachment of the organism to the respiratory epithelium (1). This may well explain the continued dissemination of the disease within immunized communities (6). Oral vaccines which stimulate local immunity in the respiratory tract (23, 24) could well prove to be more effective in decreasing circulation of the organism and the consequent spread of infection.

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## Second-generation pneumococcal vaccines

*Streptococcus pneumoniae* is a ubiquitous pathogen that causes much serious illness and death worldwide among patients of all ages (1). Infants and young children are particularly vulnerable,

especially under conditions of deprivation. Precise epidemiological data are sparse, but studies conducted in various regions of the United States (2, 3), in Scandinavia (4, 5) and in Israel (6) have provided estimates for the overall annual incidence of invasive pneumococcal infections during the first 2 years of life that range from 25 to over 150 per 100 000.

Worldwide, it seems likely that pneumococcal pneumonia alone causes more than 1 million deaths each year among young children (4), and the same organism is commonly responsible for bacteraemias and various focal infections (7). *S. pneumoniae* has recently been identified, for instance, as the most common cause among children in Finland of both acute otitis media (8) and of acute lower respiratory infections (9). It is also a frequent cause of bacterial meningitis and sinusitis. The development of a vaccine effective in young children has consequently been identified by the US Institute of Medicine as a project of high relevance, particularly for children in developing countries (10).

Some 50 years have now elapsed since capsular polysaccharides of *S. pneumoniae* were first shown to confer antigenic serotype specificity on the organism and also to protect against pneumococcal pneumonia in human subjects (11). The only pneumococcal vaccine currently marketed contains polysaccharides from 23 serotypes that account for over 90% of bacteraemic pneumococcal infections in the USA and, in a research setting, it offered more than 60% protection to experimentally-challenged immunocompetent adult subjects (12).

It has also been reported to be effective in protecting children in Papua New Guinea from serious pneumonia (13, 14). However, in general, children under 2 years of age fail to develop an effective immune response to polysaccharide antigens derived from important serotypes. By this time, they have already survived the period of life during which they are most susceptible to infection (15-17). There is evidence that these antigens — like those of *Haemophilus influenzae* (18) — are not processed by T-lymphocytes unless they are linked to a protein carrier (19).

Judging from recent experience with *H. influenzae* vaccines (see pp. 9-11), the development of a polyvalent conjugated *S. pneumoniae* vaccine could well be feasible. However, because of the bulk of the protein carrier, relatively few serotypes could be accommodated in one preparation (20). None the less, it is probable that no more than 6

specific serotypes would offer protection against the large majority of infections currently encountered within the USA (21).

Within a global context, however, important regional differences exist in the prevalence of different serotypes and these patterns have been shown to change significantly with time (22, 23). If fully effective *S. pneumoniae* vaccines are ever to become available to developing countries they must contain the relevant serotypes. This cannot be achieved until the necessary monitoring facilities, including regional reference laboratories, are in place. Few would question the cost effectiveness of such investment, but the establishment of microbiological laboratory facilities has thus far captured scant attention from the international donor community.

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## Beta-blockers and depression

The therapeutic value of beta-adrenoreceptor blockade has become acknowledged in many contexts since it became practicable with the introduction of the first of the specific beta-adrenoreceptor antagonists some 30 years ago. After an uncertain start, when pronetolol was withdrawn within a year or so of its launch on suspicion of carcinogenic potential, the clinical applications for these drugs have expanded well beyond the cardiovascular indications for which they were originally developed. Within the cardiovascular field — in which they are now used to treat hypertension, angina pectoris, secondary prevention of myocardial infarction, and dysrhythmias — they have become the most widely prescribed drugs. But they are also extensively used for a variety of other conditions, including glaucoma, hyperthyroidism, migraine, hand tremors, various anxiety disorders and aggressive psychotic behaviour resulting from organic brain lesions.

It would be surprising, having regard to the diffuse influence of adrenergic neuronal transmission on autonomic and central nervous function, if beta-blocking agents were not associated with adverse effects resulting from disturbance of vital neuro-nally-mediated functions. Short-term use is well tolerated, but there has long been doubt as to whether more prolonged use can induce clinical depression. Suggestions have been made on the basis of case reports that as many as 50% of patients receiving the standard therapeutic dose of propranolol for more than 3 months develop signs of depression (1, 2). Whether such cases are causally related to therapy or to the underlying illness has remained an issue of enduring controversy (3). Computer-based analyses of prescription records filed with Medicaid in the United States (4) and the Saskatchewan Prescription Drug Plan in Canada (5) have recently confirmed the existence of a correlation, but neither has advanced the debate on causality. In contrast, prospective case-control studies in which the diagnosis of depression

has been made on the basis of standardized rating scales have failed even to establish an association (6-8).

A further case-control study based on Medicaid records may well place the issue in clearer perspective (9). A total of over 4000 cases were selected on criteria suggestive of depressive illness: prescription of antidepressant drugs, electroconvulsive therapy, or a hospital diagnosis of depression. The files were then searched for evidence of prescription of beta-blocking drugs within the previous year, both in the cases and in matched controls. Overall, these drugs were more frequently prescribed for the case patients than for the controls (odds ratio 1.45; 95% confidence interval 1.29 to 1.62). However, when allowance was made in the analysis for several confounders (covariates — including use of benzodiazepine drugs — independently associated with beta-blocking agents and depression) the odds ratio approached unity. The authors note speculatively, by way of explanation, that sedatives and minor tranquilizers are often used by patients with depressive symptoms (10); that hypertension, whether treated or not, has been associated with depressive symptoms (11); and that a diagnosis of chronic disease has important psychological consequences for the patient (12).

Notwithstanding this reassurance, some commentators — mindful of physiological evidence linking beta-adrenergic receptors with the pathogenesis of depression (13-15) — continue to counsel caution in the use of beta-blocking drugs in the very large number of patients predisposed to this condition. It is estimated that in any 6-month period in the United States approximately 4% of all women and 2% of all men suffer severe depression (16), and that some 15% of those affected ultimately commit suicide (17). It has been suggested (3), when no effective alternative to a beta-blocking agent is available to a depressed patient, that a hydrophilic rather than a lipophilic preparation should be chosen (for example, atenolol rather than propranolol) to reduce penetration into brain tissue (18) and to reduce the risk of central adverse effects (19-21). Others might reasonably counsel, however, that the best course in treating hypertension in depressed patients, is to use captopril or another hypotensive agent that has not been prominently associated with depression.

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## Immune globulins and nosocomial infections

Some 30 years ago it was shown that regular intramuscular injections of gammaglobulin (IgG) could reduce morbidity and mortality from infections among patients with primary hypogammaglobulinaemia (1). Most patients, however, still needed frequent antibiotics even when they were receiving IgG in maximum tolerated doses. With the advent of techniques to prevent the aggregation of IgG it has become feasible to administer relatively large doses of immune globulins intravenously by infusion (2). The use of intravenous immune globulins in the prevention of pulmonary bacterial infections in young children with primary hypogammaglobulinaemia is now well established. Most of these infections are caused by *Haemophilus influenzae*, a ubiquitous organism to which most normal subjects have developed detectable levels of antibody, (see pp. 9-11) and which is consequently reliably present in the large pools of plasma now used to manufacture immune globulins (3).

Passive immunization with immune globulins specific for tetanus, hepatitis B, rabies, varicella, and cytomegalovirus has also been successful (4). These preparations, which are antibody specific, are derived from frozen plasma collected from

donors selected for their high titres of the required antibody, as measured by enzyme-linked immunosorbent assay (ELISA).

Empirical use of intravenous immune globulins in other conditions that are either immune mediated or disruptive of the immune system suggest that these plasma fractions may modulate the immune response through other, as yet undefined mechanisms (5). Notably encouraging protection against infection has been reported among patients with immune thrombocytopenic purpura (6-8), chronic lymphocytic leukaemia (9), and recipients of bone marrow transplants (10).

Their value in hospital-acquired infections in high-risk patients is less clear (4, 11, 12). Conflicting findings have been reported in two important populations of hospitalized patients: premature, low-birth-weight infants (13-18) and post-surgical patients at high risk of infection (19-20). Viewed overall — and in the absence of any apparently important differences in study design, populations studied, dosages used or methods of manufacture of the immune globulin — these inconsistencies at once "highlight the promise of passive immunization in preventing nosocomial infections as well as the inadequacy of current knowledge of the nature of the antibodies mediating protection" (21).

There is an evident problem in that most donors are unlikely to have developed protective antibody against organisms responsible for many nosocomial infections. Since concentrations and functional activities of specific antibodies to microbial pathogens can vary widely within different lots of the same preparation (4, 21), the inconsistencies in clinical responses may simply reflect variable levels of key antibodies in standard preparations (22). To meet this concern, all major pharmacopoeias are soon likely to require that each lot of gamma globulin be manufactured from pooled plasma obtained from not less than 1000 donors. Moreover, products intended for prophylaxis of hepatitis A will be required to comply with a potency test for specific antiglobulin.

Rapid advances may reasonably be anticipated in the identification and measurement of antibodies that confer protection in a wide range of nosocomial diseases. By appropriate donor selection, donor immunization, or the addition of monoclonal antibodies, it may then become possible to prepare more effective immune globulins with high and consistent levels of functional antibodies to the more common of the responsible pathogens (22).

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## Inhaled corticosteroids reduce mortality from asthma

The recent reappraisal of bronchial asthma as an essentially inflammatory condition, and the association of fatal exacerbations of the disease with intensive use of inhaled bronchodilator (beta<sub>2</sub>-agonist) drugs, has promoted the regular use of inhaled corticosteroids as the basis of preventive therapy.

Aside from the epidemiological evidence that first sensitized clinical opinion to review the therapeutic management of the condition, direct clinical evidence has emerged to indicate that intensive regular use of beta-agonists can worsen asthma (1-3) while regular use of corticosteroids is beneficial (4-6).

To complement this evidence, computerized records have been reviewed of over 12 000 patients resident in Saskatchewan, Canada between the ages of 5 and 54 years who had received 10 or more prescriptions for anti-asthma drugs between 1978 and 1987 (7). A case-control analysis was conducted within this cohort to compare the treatment prescribed for a total of 129 patients who had either died or nearly died during an acute exacerbation of asthma with a series of matched controls. After adjustment of differences in the use of other anti-asthma drugs and for the number of prior admissions to hospital, there was evidence that patients who received one or more metered-dose inhalers of beclomethasone monthly over one year — which corresponds to some 200 inhalations of 100 micrograms monthly — tended to have more severe asthma than patients in the control groups. Yet, over the period of observation, they were apparently exposed to a significantly lower risk of fatality or near-fatality (odds ratio, 0.1; 95% confidence interval, 0.02 to 0.6).

It is rarely possible, in such studies, to ascribe a causal relationship to a therapeutic intervention and a putative response with assurance. Another possible explanation of these findings — which is conceded by the authors — is that patients taking corticosteroids regularly were also receiving better overall care. However, the most straightforward interpretation is that sufficient use of inhaled corticosteroids reduces the likelihood of a sudden overwhelming exacerbation. Indeed, the data suggest that doses less than those now widely recommended exert a strong protective effect against serious exacerbations. They also unequivocally endorse the emphasis now placed on regular

use of inhaled corticosteroids in recently revised national therapeutic guidelines on the management of chronic persistent asthma (8, 9).

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## Antidepressant drugs and the risk of suicide

It has been estimated that in the United States, a quarter of all patients with major depressive illness attempt suicide during their life and that, as a result, some 15% of these patients eventually die (1-3). In 1986, over 30 000 suicidal deaths were reported in

the USA (4). About one in two of these patient incidents involved a previously-diagnosed major depression, and one in five of these cases was attributed to drug overdose (4) — often of the antidepressants used to treat the causal illness (4-6).

In Europe, several studies based on national poisoning statistics and national prescribing records collected in the mid-1980s suggest that tricyclic antidepressants, in general, are associated with a significantly higher rate of deaths from suicide than some of the newer nontricyclic compounds (7-11). In particular, three studies from the United Kingdom indicate that use of the tricyclic antidepressants amitriptyline, imipramine, nortriptyline, and desipramine is associated with a higher incidence of suicidal deaths than either mianserin (7-9) or trazodone (7); while two studies from Scandinavia similarly conclude that amitriptyline and doxepin each carry a higher risk than mianserin (10, 11).

These studies have now been complemented in the United States by an analysis of prescription use of antidepressant drugs nationwide and of published information on drug-related suicides that was derived from two independent data bases during the biennium 1989-1990 (12). The results obtained with each of these data sets are consistent in indicating that deaths from suicide are associated more strongly with tricyclic antidepressant drugs than with non-tricyclics, and that this difference may reflect a higher risk of fatality following overdosage rather than a higher incidence of suicidal attempts.

The risk of death following overdosage was apparently higher for products containing tricyclic compounds as compared with nontricyclic products. It was greatest for products containing desipramine for which the comparative risk of death following overdosage was estimated to be 17-fold greater than with trazodone, and 8.5-fold greater than with fluoxetine. The apparently greater toxicity of the tricyclics was not unexpected since it could well reflect their known dysrhythmic properties, anticholinergic effects, and their sedative effect on the central nervous system (13-16). The newer antidepressants (fluoxetine, trazodone, and mianserin hydrochloride) do not appear to be directly cardiotoxic and have less anticholinergic activity (14-16).

Desipramine, a secondary-amine tricyclic compound, has generally been regarded as safer than tertiary-amines (17-19). The possibility that it is associated in overdosage with a greater risk of

death than amitriptyline, imipramine and other tertiary-amine tricyclic compounds was unexpected, although similar findings have been reported elsewhere (8). By way of explanation, the authors suggest that desipramine may be uniquely cardiotoxic in overdosage (although they advance no evidence for this); that its relative lack of anticholinergic activity may promote rapid absorption following overdosage; and that, because of its reputation as a relatively safe antidepressant, it tends to be selectively prescribed for medically vulnerable patients.

None of these hypotheses can be tested on the basis of the available data. The results obtained should inspire the organization of further surveys. As the authors of this study explain, the approach to such investigations would be placed on a firmer basis by the creation of data bases that are able to provide more precise data on the exact number of patients using each drug within the defined population. In the absence of this information, precise statistical analysis of inter-drug differences in the possibility of suicide and suicidal attempts is precluded.

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