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We may return unduly long letters to the author for shortening so that we can offer readers as wide a selection as possible. We receive so many letters each week that we have to omit some of them. Letters must be signed personally by all their authors. We cannot acknowledge their receipt unless a stamped addressed envelope or an international reply coupon is enclosed.

Measles again

SIR,—We take strong issue with several of the opinions expressed by Dr Hillis Smith regarding the control and elimination of measles (15 March, p 766). These opinions ignore the achievements of organised measles control programmes such as the United States' effort to eliminate measles. Reported measles activity during 1979 (13 448 cases provisional total) is the lowest ever reported in the United States, representing a decrease of 50% from the 1978 total and a 97% decrease from the total in 1962, the year before measles vaccine was licensed.

Dr Smith's argument for a selective immunisation policy is in part based on the belief that there has been a major increase in cases among adults. It is true that a larger proportion of measles cases occur in adolescents and young adults now than was the case before vaccine was available. However, this is a result of more striking decreases in incidence for younger age groups. All age groups have had significant declines in incidence: if we compare the period 1960-4 with 1976-8, there has been a 94% decline in reported incidence for those under 10 years of age, a 55% decline for those aged 10-14 years, and a 40% decline for those 15 years of age and older. Dr Smith also argues that there is waning immunity to measles for older age groups. However, published data show that the live measles virus vaccines induce excellent levels of haemagglutination-inhibition antibody, which persist at least 14 years after vaccination¹ and that protection from exposure to measles does not wane significantly with time.^{2,3} Although cases of measles do occur in persons who have been vaccinated, investigation usually reveals that the majority of these persons were vaccinated before 1 year of age or received killed virus vaccine.

Dr Smith cites one investigation which describes adverse reactions experienced by

adult vaccine recipients.⁴ A major limitation of this study is the lack of a control group, a problem acknowledged by one of the investigators.⁵ Moreover, in two studies of adult vaccinees which did include controls, there was no significant difference between vaccinees and controls in the incidence of serious reactions after measles vaccination.^{6,7}

Finally, we believe that it is important to emphasise the shortcomings of Dr Smith's proposal for a programme of "selective immunisation." Although such a programme might give protection to a limited number of children with certain underlying illnesses it ignores the serious complications of measles, for which susceptible healthy children are still at risk. These complications, which may be either immediate (for example, pneumonia, encephalitis) or delayed (for example, subacute sclerosing panencephalitis), can be prevented by vaccination.⁸ Moreover, it is unlikely that a selective programme would have a major impact on measles-associated mortality in England and Wales, which experienced an annual average of 25.6 such deaths from 1970 to 1977.⁹ In contrast, the annual average number of deaths attributed to measles in the United States in the same period was 36.6, even though the US population is more than four times greater than that of England and Wales.

In conclusion, we believe the progress to date proves that a plan to eliminate measles from the United States cannot be dismissed as merely a "Utopian ideal." Measles elimination is a realistic, safe, and humanitarian goal.

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- ¹ Krugman S. *J Pediatr* 1977;**90**:1-12.
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- ³ Shelton JD, Jacobson JE, Orenstein WA, et al. *Pediatrics* 1978;**62**:961-4.
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- ⁵ Preblud SR, Herrmann KL, Bernier RH, Brandling-Bennett AD. *Ann Intern Med* 1980;**92**:132-3.
- ⁶ Center for Disease Control. *Morbidity and Mortality Weekly Rep* 1979;**28**:553-4.
- ⁷ Center for Disease Control. *Morbidity and Mortality Weekly Rep* 1980;**29**:21-2.
- ⁸ Modlin JF, Jabbour JT, Witte JJ, Halsey NA. *Pediatrics* 1977;**59**:505-12.
- ⁹ World Health Organisation. *World Health Statistics Annual 1970-9*. Geneva: WHO.

SIR,—Dr Hillis Smith (15 March, p 766), impressed by the US reports on adult measles, suggests that in developed countries where acceptance of measles vaccine is insufficient to achieve near-eradication of the disease it might be better to vaccinate only children at special risk, who admittedly will be difficult to select.

This view could be a matter of consideration if there was proof that live vaccine-acquired protection does wane after a number of years; but, 17 years after the beginning of routine immunisation in the United States, there is no such proof. All cases of measles in the United States can be explained by lack of vaccination, by vaccination with killed vaccine, or by failure of live vaccine to take. This occurs in less than 10% under normal conditions, and at a higher percentage when the vaccine has been improperly handled or has been given in the presence of maternal antibody or with immune serum globulin. The excellent persistence of antibody titre after 10 years in individuals who seroconverted after live measles vaccine¹ further increases the prospect that protection against clinical disease will be as long lived after successful vaccination as following natural infection.

The decrease of measles virus circulation due to mass vaccination may have caused a

number of susceptible individuals to become exposed as adults rather than as children. This problem does not attain unmanageable proportions, since the incidence of measles in the older age groups has remained lower in the United States than it was before the vaccination era. A proportional shift of the remaining cases to older age groups did occur and this was predictable, as it was with other diseases that the young are vaccinated against. From the reports to the Center for Disease Control, Atlanta, it appears that in 1960-4 37% of measles cases occurred under the age of 5 years, 53% at 5-9 years, 7% at 10-14 years, and 3% at and above 15 years of age. In 1971-5, the figures were 35%, 34%, 18%, and 14% respectively, and in 1976-8 16%, 25%, 36%, and 24%. During the prevaccine era, about 500 000 cases of measles were reported each year.² In 1979, only 13 000 cases were reported.³ On the basis of these figures, before vaccine was used about 50 000 reported cases of measles occurred after 10 years of age, compared with only about 8000 in this age group in 1979. Similarly, before vaccine was used 15 000 cases were reported in persons over 15 years of age, compared with about 3000 in 1979. If the present trend continues, there should be less than 10 000 reported cases of measles in the United States in 1980. The number of cases in adults will thus continue to be much less than in the prevaccine era.

A country can always decide to further decrease virus circulation, and exposure of adults, by more intensive vaccination of the young, as has been the effect of the US policy. For all these reasons it is not justified to withhold the personal benefit of the vaccine from the average child in any developed country. Of course, adult measles is highly visible owing to the absence of cases in the vaccinated young. Adult measles should be an incentive not to limit vaccination programmes to the recommended age of 15 months, but to extend them up to the age of 12 years in children who have never had measles or the vaccine.

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¹ Weibel RE, Bunyak EB, McLean AA, Hilleman MR. *Proc Soc Exp Biol Med* 1979;162:328-32.

² Orenstein WA, Halsey NA, Hayden GE, et al. *J Inf Dis* 1978;137:847-53.

³ Anonymous. *Morb Mort Wkly Rep* 1979;28:410-1.

SIR,—Dr Hillas Smith (15 March, p 766) has drawn attention to *selective* immunisation against measles, which was proposed in 1968 as an alternative to *routine* introduction of vaccine.¹ As he rightly points out, with the present acceptance rates of immunisation of the child population, measles is moving into the older age groups as was predicted.^{1,2} While the vaccine appears to be about 95% effective, the duration of protection is not known, nor is it known if revaccination may be required for adults (in whom vaccine reactions are more severe). We also know very little about possible teratogenic effects of "wild" or vaccine viruses in pregnant women.

Even before vaccine was introduced, measles appeared to be becoming a trivial disease in civilised communities, and it seems

not unreasonable to hope "that it will rapidly become as mild as rubella and chickenpox with a negligible mortality."³ There is something to be said for allowing a mild "wild" measles virus to give a natural life-long protection to the healthy children of the community and to offer vaccine *selectively* to those among whom the greatest morbidity and mortality occurs or who have escaped a natural infection in the early years of childhood.

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¹ Dick GWA. *The scientific basis of medicine annual reviews*. London: Athlone Press, 1968:89.

² Rand KH, Emmons RW, Merigan TC. *JAMA* 1976;236:1028.

³ Paul H. *The control of diseases*. Edinburgh: ES Livingstone, 1964:93.

Tuberculosis in patients having dialysis

SIR,—We believe that the recommendations you proposed in your leading article (9 February, p 349) for the treatment of patients on regular dialysis are misleading and potentially dangerous.

Firstly, we think that the dosage of isoniazid should not be decreased from 300 mg a day. Isoniazid is predominantly eliminated by acetylation in the liver and as a consequence the unchanged drug does not accumulate in renal failure. From estimates of the proportions of the dose excreted unchanged in the urine by normal subjects,¹ we calculate that the half life of isoniazid in slow acetylators is likely to be increased only from about three to four hours in complete renal failure, while in rapid acetylators changes in its rate of elimination would be minimal. Acetylisoniazid is eventually converted to diacetylhydrazine and isonicotinylglycine and in our experience the accumulation of these non-toxic terminal metabolites between dialyses does no harm.² Loss of renal function would have a negligible effect on peak isoniazid plasma concentrations, with which the antituberculous efficacy of the drug is correlated.³ In contrast, lowering the isoniazid dose size would certainly result in suboptimal drug concentrations and, if the patient were particularly heavy, a dose of 150 mg, as recommended, might even be ineffective.

Secondly, if it were considered important to add a third drug to the combination of isoniazid and rifampicin for the treatment of dialysis patients, it would be unwise to prescribe ethambutol at a daily dose of 5 mg/kg. Although the average plasma concentrations attained after several days of this dosage would probably be similar to those following dosage with 25 mg/kg/day in patients with normal renal function,³ the concentrations during the first one to two days would be much lower. As ethambutol in a daily dose of 6 mg/kg/day is only partially effective,⁵ a patient typically being dialysed three times a week and given 5 mg/kg/day would be unlikely to be getting fully effective therapy. We would therefore recommend giving substantially larger doses of ethambutol four to six hours before each dialysis as a safe and effective way of using this drug in renal failure. For patients being dialysed three times or more each week a dose of 25 mg/kg ethambutol might be employed, the dose being increased to 45 mg/kg for twice-weekly dialysis and 90 mg/kg for once-weekly dialysis. Daily doses of 25 mg/kg ethambutol are routinely used for the initial treatment of normal patients and the larger doses have been

shown to be well tolerated and efficacious in controlled clinical trials when given intermittently.^{6,7}

Since the efficacy of ethambutol in dialysed patients has not been established, it might be preferable to give streptomycin, an inherently more potent drug, in its place. Streptomycin could be given at a conventional dosage of 0.75 g four to six hours before each dialysis. The clinical efficacy of intermittent streptomycin treatment in patients with normal renal function has been well documented⁸ and since such a regimen is likely to be well tolerated in dialysis patients it can be utilised without recourse to serum streptomycin measurements. In brief, we recommend that tuberculous patients having dialysis should receive daily isoniazid and rifampicin at full conventional dosages, supplemented if it is thought necessary by streptomycin or ethambutol given four to six hours before dialysis, neither drug being administered in a reduced dosage.

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¹ *J Pharmacokinet Biopharm* 1976;4:83-113.

² Ellard GA. *Bull Int Union Tuberc* 1976;51:143-54.

³ Mitchison DA. In: Davies DS, Prichard BNC, eds. *Biological effects of drugs in relation to their plasma concentration* (British Pharmacological Society). London: Macmillan, 1973.

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⁵ Doster B, Murray FJ, Newman R, et al. *Am Rev Respir Dis* 1973;107:177-90.

⁶ Sbarbaro JA, Hudson LD. *Am Rev Respir Dis* 1974;110:91-4.

⁷ Tripathy SP. In: *Symposium on Rifampicin in Tuberculosis Treatment*. Helsinki: Uudenmaan Kirjapaino Oy, 1974:91-102.

⁸ Fox W. *Chest* 1979;76, suppl:785-96.

* * * Is it legitimate to accept a calculated change in the half life of isoniazid in renal failure from three to four hours on the basis of data from normal subjects? Maher¹ reported an increase in half life of isoniazid from the normal two to six hours to up to 17 hours in renal failure. On the basis of this prolonged half life, most recommend the limitation of dose to 150 mg daily in view of the risk of peripheral neuropathy.² But, as we said in our leading article, higher doses may be used if plasma concentrations are measured,³ and the larger patient would usually warrant a higher dose. In their comments on ethambutol Drs Mitchison and Ellard give their own answer to their criticism of our recommendations. If the drug is given in the dose of 5 mg/kg continuously in renal failure concentrations will be low on the first day after dialysis but will reach satisfactory concentrations before the next dialysis; and, as they say, intermittent peaks are efficacious. Anderson *et al*⁴ recommended that ethambutol should be given either in a dose of 18 mg/kg between dialyses or in a daily dose of 5 mg/kg. We recommend the latter because most patients find it easier to remember to take a regular daily dose.

Drs Mitchison and Ellard's suggestions about streptomycin would create practical problems. The patient with tuberculosis who is on dialysis will often have poor muscle bulk, which makes intramuscular injection difficult and painful. In addition, anticoagulation is necessary for dialysis and if an intramuscular injection has been given within the previous six hours a haematoma is likely. Furthermore, nephrologists are only too aware of the long-term ototoxicity associated with streptomycin,