Bauer's view, but a subsequent trial in Pakistan[4] failed to demonstrate a statistically significant effect. In addition Rao *et al.*[5] in a controlled and supervised trial with a closely related compound, shown to be highly effective in the laboratory, were able to show only a minimal prophylactic effect. If the thiosemicarbazones are really as effective against variola virus in man, as Dr. Bauer claims, it is surprising that they have no appreciable effect on the success rate of vaccination with the closely related vaccinia virus.[6]

Until more conclusive evidence is presented in favour of hyperimmune gammaglobulin and antiviral drugs of the thiosemicarbazone series we consider that vaccination with all its limitations must remain the first line of defence in containing outbreaks of smallpox. In our view this should be combined with hyperimmune gammaglobulin for those at particular risk. At the present time we do not believe that thiosemicarbazones have a part to play in the routine prophylaxis of smallpox.—We are, etc.,

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Chloride and Cancer

SIR,—I could not help feeling that your otherwise well-balanced leading article on this subject (30 March, p. 590) tended to oversimplify two problems. Reference is made to the induction of sarcomas at the site of subcutaneous implantation of plastic films and it is suggested that tumour induction is dependent on the "uninterrupted area of the film." This is not universally true and the possible importance in relation to cancer induction of chemical agents that can be leached out of plastics has not been ruled out.[1] Plastic sponge is potently productive of sarcomas on implantation[2] and fragmented polyethylene proved just as potent as a solid piece of the same material in producing sarcomas.[3] Also other factors such as the relative numbers of anions and cations may be important.[4] In any case, in the light of the work of Grasso and Golberg[5] few authorities in the field of experimental carcinogenesis would now accept the induction or non-induction of sarcomas in the subcutaneous tissues of rats in response to the subcutaneous injection or implantation of foreign materials as providing information that is indicative either of safety or hazard for man of materials to which he is not exposed by a parenteral route. On the other hand, an interpretable and useful observation from this kind of experiment in the case of polyvinyl chloride would have been that acoustic duct tumours did or did not occur in rats bearing implants.

That there is a need for a series of simple inexpensive tests which suggest that some substances are more likely to be carcinogens than others is indisputable. Nor would one reject the view that short-term in-vitro studies may be of value in warning that substances may be carcinogens and in the elucidation of mechanisms of carcinogenicity.[6] But what must be disputed is whether mutation of a micro-organism of transformation of cells in vitro should be regarded as reliable evidence of carcinogenicity. The reliability of such short-term tests for predicting carcinogenicity needs to be assessed and the false-positive and false-negative rates ascertained. Unfortunately this can only be done laboriously by comparing the results of short- and long-term tests. Where this has been done in the past the approach has generally been to show that known, usually potent, carcinogens give positive results in short-term tests, and even this has not always proved easy. The opposite approach—namely, of seeing whether substances which give rise to weekly positive results in short-term tests or which unexpectedly give rise to positive results predispose to neoplasia in the long term—has rarely been followed.

Clearly much more thought is going to have to be used to protect workers against possible cancer hazard from new chemicals and materials used in industry, but confusion and little benefit would result from falsely labelling substances as carcinogens on the basis of short-term tests of unproven validity. Committees of experts that have reviewed carcinogenicity testing during recent years have invariably rejected short-term tests for the purpose of establishing safety.[8,9] We should be equally careful to reject them for the purpose of establishing hazard.—I am, etc.,

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Amitriptyline and Imipramine Poisoning in Children

SIR,—Drs. K. M. Goel and R. A. Shanks (16 February, p. 261) outline the numerous dangers of tricyclic antidepressant overdosage and sound a very timely warning on the folly of prescribing such drugs for children. I am concerned, however, that they should state that there is "no known antidote." Much more alarming is the letter from Drs. D. A. Price and R. J. Postlethwaite (23 March, p. 575) advocating the use of parenteral diphenylhydantoin in patients poisoned with these drugs. It is evident from such communications that experience in the management of tricyclic antidepressant poisoning is limited, as Dr. Price and Postlethwaite admit.

The antidote available for tricyclic antidepressant poisoning is physostigmine salicylate was first described by Slovis *et al.*[1] in 1968 followed by Rumack[2] in 1973. In the near future this agent will be recommended by drug companies marketing tricyclic antidepressants for use in the event of overdosage. It is important that a critical appraisal of this form of treatment should be made available.

In this centre we recently treated with physostigmine salicylate 21 consecutive patients with acute tricyclic antidepressant poisoning. In this series unconsciousness, hyperreflexia, bilateral extensor plantar responses, and the classical peripheral and cholinergic effects were all rapidly reversed—a clear indication that physostigmine salicylate is an antidote in tricyclic poisoning. On the other hand, though 409 patients with tricyclic antidepressant poisoning have been admitted to this centre during the past five years no fatalities have been encountered using the conservative supportive regimen described by Matthew and Lawson.[3] Physostigmine has thus no place in the *routine* management of such patients. This statement is supported by the occurrence of potentially dangerous side effects associated with administration of the drug. In our series two of the 21 patients had convulsions and two others hypersalivated and developed a severe bradycardia due to cholinergic action. Despite these dangers physostigmine is of value in severely poisoned patients where other medical complications demand that the period of unconsciousness should be shortened.—I am, etc.,

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SIR,—The letter from Drs. K. M. Goel and R. A. Shanks (23 March, p. 575) in reply to Dr. R. N. Wilson's criticism (9 March, p. 455) unfortunately indicates that the authors themselves have not quite appreciated the significance of their own paper. Dr. Wilson has clearly pointed out the consequence of not distinguishing between inadvertent (accidental) ingestion and deliberate, planned (therapeutic) ingestion. In fact in their original paper (16 February, p. 263) Drs. Goel and Shanks have themselves fallen into this error for they state that "children who ingest tricyclics *in whatever dosage* [my italics] should always be admitted for observation and continuous cardiac monitoring for 24 hours, because arrhythmias in these cases are common and dangerous." By saying this they include all who are being treated for enuresis too.

Dr. Wilson says that the *Daily Mirror* article conveys the impression that the therapeutic dose was to blame. How could the *Daily Mirror* be blamed if the authors did not make the distinction between thera-

Abstracts of papers submitted for publication on the Mortality Study of Workers exposed to Vinyl Chloride Monomer.

(A) THE MORTALITY EXPERIENCE OF WORKERS EXPOSED TO VINYL CHLORIDE MONOMER IN THE MANUFACTURE OF POLYVINYL CHLORIDE IN GREAT BRITAIN

By A.J.FOX and P.F.COLLIER

Identification particulars were obtained for over 7,000 men who were at some time between 1940 and 1974 exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride. Approximately 99% of these have been traced and their mortality experience studied. The overall standardised mortality ratio, 75.4, shows a significant reduction compared with the national rates. Four cases of liver cancer are found. Two of these have been confirmed by a panel of liver pathologists as angiosarcoma and two as not angiosarcoma. There is no evidence supporting the hypothesis that cancers other than those of the liver are associated with exposure to vinyl chloride monomer. The two cases of angiosarcoma were found in men who has been exposed to high concentrations although the second man died only eight years after exposure. The industry in Great Britain has expanded considerably since the Second World War with over 50 per cent of men having entered within the last decade. Conclusions drawn about the influence of vinyl chloride monomer on the mortality experience of men in this industry must consequently be tempered by the reservation that the full impact may not yet be in evidence.

(Submitted to the British Journal of Industrial Medicine)

(B) LOW MORTALITY RATES IN INDUSTRIAL COHORT STUDIES DUE TO SELECTION FOR WORK AND SURVIVAL IN THE INDUSTRY

By A.J.FOX and P.F.COLLIER

Occupational groups are often described as relatively healthy because their mortality rates are lower than the national average. Although correct this confuses the issue for those interested in assessing the effects of exposure to a particular chemical. By a further analysis of data collected in a study of all men ever exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain, three factors have been shown to contribute to the low mortality rates that were observed. The three factors, the selection of a healthy population for employment; the survival in the industry of the healthier men; and the length of time that this population has been pursued, have all been quantified. The mortality experience within five years of entering this industry was shown to be as low as 37 per cent of that expected; for circulatory disease and respiratory disease as low as 21 per cent. There was a progressive increase in standardised mortality ratio with the length of time since entry such that the effect had almost disappeared 15 years after entry. To avoid confounding the selection effect with the survival effect the latter was measured by separating men who survived 15 years after entering the industry according to whether or not they were still in the industry after this period. Those who had left experienced an overall standardised mortality ratio some 50 per cent higher than those still in the industry. This effect although consistent in the age groups between 25 and 74 and all cause groups studied was greatest in those aged between 25 and 44 and for lung cancer and respiratory disease.

(Submitted to the British Journal of Preventive and Social Medicine)

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