munological processes may play a part in the causation of pre-eclampsia, together with your leading article (p. 468). Curiously enough Dr. W. B. Patterson has just sent me his book¹ in which he notes the association of fetal hyperplasia with late pregnancy toxæmia.

It has always amazed me that attempts are still being made in this cybernetic era to pinpoint one lesion as being the cause of, or always being associated with, pre-eclampsia and presumably eclampsia. Normal healthy life is entirely dependent on the adequate functioning of homeostatic mechanisms and surely the wonder must be not that a relatively few pregnant women get pre-eclampsia, but rather that at least 85% of all pregnant women throughout the world can adjust to its demands. For consider that it is not yet understood why the mother does not immunologically reject the fetus, why her vascular system tolerates the vastly increased amounts of the steroid hormones, or how she overcomes the metabolic and mechanical stresses and strains of pregnancy. It is only necessary to recall the effects of hormonal stimulation on the spiral arteries during the menstrual cycle to recognize the potential vulnerability of small vessels to excessive hormonal influence.

The symptoms associated with "glomerular endotheliosis" are clinically indistinguishable from those associated with chronic glomerular nephritis. So much for precise lesions. Further, the multigravida rarely manifests hypertension, proteinuria, and oedema unless she had these symptoms during her first pregnancy and yet electron microscopical studies of material removed at renal biopsy from 152 multiparae revealed no detectable lesion or renal abnormality in half the cases.² It would appear to follow that "glomerular endotheliosis" is a lesion which is most commonly seen in first pregnancies, clears up completely, and is unlikely to recur in subsequent pregnancies, even though the signs and symptoms of pre-eclampsia may. Then too, in another leading article in the same issue (p. 470), you draw attention to the fact that it is not at present known "whether autoregulation occurs in essential hypertension and, if it does, whether it can account for the variations in plasma volume."

The main object of pregnancy is to produce a viable, healthy child, and if its nutrition is at stake, whether because of defective kidneys or an inadequate placenta, feed-back mechanisms are called into play and, in extreme cases, provoke undesired symptoms and lesions. McCartney² does not think that glomerular endotheliosis causes pre-eclampsia and neither do Dixon and Robertson^{3,4} or Brosens,⁵ regard atherosclerosis of the spiral arteries in the placental bed as a causal factor. Incidentally, Robertson observed during the course of conversation that the closest approximation he had seen to the vascular changes he had observed in the blood vessels of the placenta bed were those occurring in syphilitic lesions. It is consequently reasonable to observe that the lesions resulting from a break-down of a homeostatic mechanism, whether in the liver, kidney, placenta, or brain, may not always be identical and conversely that apparently identical lesions may be produced in different ways.

Eclampsia is a syndrome and consequently no single cause for it will ever be dis-

covered. The fact remains that whereas there were over 400 maternal deaths from pregnancy toxæmia in England and Wales during 1934, there were probably not more than four last year. This fall is due to improved antenatal care (including antenatal nutrition and rest) and the induction of labour at about 38 weeks in patients with hypertension. This was made possible only by the discovery of the antibiotics and by the introduction of the oxytocin drip. It is suggested that most of the women who get pre-eclampsia in this country had defects, whether detectable or occult, before pregnancy started. The ultimate control of both the hormonal and autonomic systems is vested in the hypothalamus and this control is largely determined in extent by the integrity of the vascular system, the endocrine organs, and the kidneys.—I am, etc.,

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- 1 Patterson, W. B., *Fetal Adrenal Hyperplasia; Its Relationship to Late Toxemia*. Published by the author, 1973.
- 2 McCartney, C. P., *Gynaecologia*, 1969, 167, 214.
- 3 Dixon, H. G., and Robertson, W. B., *Journal of Obstetrics and Gynaecology of the British Empire*, 1958, 65, 803.
- 4 Dixon, H. G., and Robertson, W. B., *Pathologia et Microbiologia*, 1961, 24, 622.
- 5 Brosens, I. A., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1964, 71, 222.

SIR,—Further to the interesting article by Dr. O. M. Petrucco and others (16 March, p. 473), I would like to report the results of some immunofluorescent antibody studies performed using placenta, maternal sera, and human kidney. The latter was removed from a 32-year-old parous patient shortly after a fatal accident. Histological assessment revealed the renal tissues to be entirely free of any disease, and as far as could be determined the patient had had no previous history of renal disease. Maternal serum was collected from pregnant patients at delivery who had had a normal antenatal period and from patients with pre-eclampsia. A section of the placenta was also obtained after each delivery. Sections 4 μ m thick of placenta and renal tissue were used for immunofluorescent antibody study, fluorescein-labelled anti-IgG, -IgA, and -IgM being used for staining purposes. Specificity of the antisera was checked by "blocking" studies.

Immunofluorescent staining without prior incubation with the respective maternal serum revealed no evidence of antibody deposition. But if incubation with maternal serum was performed before the immunofluorescent staining some interesting results were obtained. In the normal patients no specific fluorescence was seen either in the placenta or renal tissues. But in patients with pre-eclampsia marked IgM deposition was noted in the fetal capillaries in the placenta and in the proximal renal tubular epithelium, but none in Bowman's capsule. Moreover, if serum from a normal patient was incubated with a placenta from a toxæmic patient no specific fluorescence was seen. If serum from a toxæmic patient was incubated with tissues from a normal patient the areas of IgM deposition were demonstrated as described earlier. IgG deposition was found in similar areas but was very much less dense.

These findings would support Curzen's¹ concept of the presence of trophoblast-specific antibodies in patients with pre-eclampsia which cross-reacted with kidney tissues. From the above evidence they appear to localize in the proximal renal tubule. This part of the tubule is responsible for Na⁺, Cl⁻, HCO₃⁻, and H₂O homeostasis, and if damaged could disturb the balance, possibly leading to some of the changes noted clinically in pre-eclampsia. How this "autoimmune" process is triggered is difficult to determine. Presumably there is a breakdown in the "barrier" protecting the fetus from rejection by the mother.

These findings, in conjunction with those reported by Dr. Petrucco and his colleagues—namely, the constant finding of IgM, IgG, and complement deposition together in the glomerulus and its vascular supply—would lend support to the hypothesis that an immunological process plays a part in pre-eclampsia.—I am, etc.,

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- 1 Curzen, P., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1968, 75, 1128.

Vaccination of Smallpox Contacts

SIR,—We cannot allow to pass unchallenged the views on the control of smallpox expressed by Dr. D. J. Bauer (23 March, p. 576). All concerned with the management of smallpox know that vaccination during incubation cannot be relied on to protect, but it does not follow that it is without value. There is good evidence that successful primary vaccination in the incubation period will modify the severity of the attack and reduce mortality by half.¹ The effect on the incidence of smallpox is less certain, but Dr. Bauer quotes a 56% attack rate in unvaccinated primary contacts who remained unvaccinated as against a 19% rate in previously unvaccinated contacts who received vaccination after diagnosis of the index cases. Active immunization by vaccination has been the first-line defence against smallpox for many years and has not only proved successful in eradicating the disease from endemic areas but has also succeeded in containing infection when re-introduced. This is a matter of such importance that it is essential to consider the evidence with the utmost care before adopting passive immunization and chemoprophylaxis as the optimum protection for contacts.

The much-quoted trial by Kempe *et al.*² in 1956 on the prophylactic value of hyperimmune gammaglobulin had serious defects, but a subsequent trial in 1961³ produced more convincing evidence of the value of this procedure in conjunction with vaccination. The position with the thiosemicarbazone group of drugs is more uncertain. The trial of methisazone by Bauer *et al.*,⁴ which suggested a fourfold reduction in incidence, is open to criticism. The treatment and control groups were not allocated at random, those refusing treatment being assigned to the control group, and supervision of contacts was inadequate. A further trial of this compound in variola minor by de Valle *et al.*⁵ supported Dr.

Bauer's view, but a subsequent trial in Pakistan⁶ failed to demonstrate a statistically significant effect. In addition Rao *et al.*⁷ 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.^{4,7}

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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Vinyl 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 potentially productive of sarcomas on implantation² 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^{5,6} 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.⁷ 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 over-dosage 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 Drs. Price and Postlethwaite admit.

The antidote available for tricyclic antidepressant poisoning is physostigmine. It was first described by Slovits *et al.*¹ in 1971 followed by Rumack² in 1973. In the near future this agent will be recommended by drug companies marketing tricyclic antidepressants for use in the event of over-dosage. 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 anticholinergic 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 this 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-