question the reasons for this, and it may be relevant that disordered coagulation has been described in both a mother¹ and a baby² following feto-maternal bleeding.

We have shown³ that, before the thirty-sixth week of gestation, women who are to become hypertensive are recipients of more frequent and larger transfusions of fetal blood than women who remain normotensive throughout pregnancy.³ The placentae from 114 primiparae in this prospective study were examined, applying the method of Aherne and Dunnill for the assessment of macroscopic infarction,⁴ and a statistically significant difference was found between the two groups (Table). We postulated that in women who were to become pre-eclamptic changes occurred in the placental vasculature in early pregnancy, that the presence of fetal cells in the maternal circulation was an indication of placental breakdown, and that subsequent coagulation within the placenta resulted in infarction.⁵ The hypercoagulable state of the woman in late pregnancy predisposes her to intravascular coagulation, and it seemed rational to suggest that this could result from placental thromboplastin release with the results that have now been described by Dr. Bonnar.

Incidence of Macroscopic Placental Infarction in 28 Hypertensive and 113 Normotensive Pregnancies.

	Hypertensive Pregnancies	Normotensive Pregnancies
Placentae Infarcted	17	40
Placentae not Infarcted	11	73

Total 141; $\chi^2=5.97$; $df=1$; $P<0.025$

With regard to the absence of fibrin degradation products in the epileptic patient examined by Dr. Bonnar, we were unable to demonstrate fetal bleeding as a consequence of major fits in two women in our survey.

As a result of our findings we suggested that measures to enhance fibrinolytic activity might benefit those women who, because of previous history, abnormal weight gain, or demonstrable large fetal bleeds early in the third trimester were candidates for pre-eclampsia, and that heparin might be of value in those with the clinical syndrome.

The factors acting in the early pregnancies of pre-eclamptic women are unknown, but differences in familial and racial incidence suggest that certain women are predisposed to the disease, and the higher incidence in primiparae may be because some of the susceptible group do not proceed to further pregnancies.—I am, etc.,

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¹ Chown, B., *American Journal of Obstetrics and Gynecology*, 1955, 70, 1298.

² Samet, S., and Bowman, H. S., *American Journal of Obstetrics and Gynecology*, 1961, 81, 49.

³ Jones, P., McNay, A., and Walker, W., *British Medical Journal*, 1969, 3, 738.

⁴ Aherne, W., and Dunnill, M. S., *Journal of Pathology and Bacteriology*, 1966, 91, 123.

⁵ Jones, P., M.D. Thesis, University of Newcastle upon Tyne, 1968.

Chronic Phenacetin Nephropathy

SIR,—I strongly support the views and comments of Professor H. E. de Wardener and Dr. K. G. Koutsaimanis (3 April, p. 45) concerning the probable roles of phenacetin and aspirin in the renal medullary necrosis of analgesic abuse. Their figures of the total annual consumption of phenacetin and aspirin strongly suggest that, if aspirin had anything to do with renal medullary necrosis, the incidence of the syndrome would be double what it is and a substantial proportion would arise from consumption of aspirin alone un-mixed with other analgesics.

As I have previously pointed out in your columns¹ and elsewhere², phenacetin is the only common component of the numerous drug combinations implicated in this syndrome. Several of the phenacetin-containing mixtures used in Europe, for example Saridon, do not contain any aspirin at all. Until and unless the contrary is proved, it is only natural that phenacetin should be blamed for the syndrome. Phenacetin, in this context, includes its concomitant impurities such as acetic-4-chloranilide and its effective metabolite paracetamol. Paracetamol may eventually prove to be the agent responsible for the renal medullary damage, in which case the substitution of paracetamol for phenacetin in analgesic mixtures could not be expected to have any effect in reducing the incidence of "analgesic" nephropathy.

I have always referred to this syndrome as "chronic phenacetin nephropathy" and I consider that the qualifying word "chronic" should properly be used, whether one chooses to refer to the syndrome as "analgesic" or "phenacetin" nephropathy. After all, the disease is fundamentally chronic and insidious and results from prolonged drug abuse. It used to be called "primary chronic interstitial nephritis" until it was shown that the renal parenchymal atrophy in this syndrome was due, not to any primary interstitial nephritis, but to parenchymal atrophy and fibrosis consequent upon the medullary necrosis.^{2,3}—I am, etc.,

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¹ Sanerkin, N. G., *British Medical Journal*, 1964, 1, 980.

² Sanerkin, N. G., *British Journal of Urology*, 1966, 38, 361.

³ Dawborn, J. K., Fairley, K. F., Kincaid-Smith, P., and King, W. E., *Quarterly Journal of Medicine*, 1966, 35, 69.

Clofibrate

SIR,—Your article in the Today's Drugs series (12 September, 1970, p. 632) clearly was written by an expert with a profound experience of the drug. Nevertheless I feel it is necessary to make two comments.

You write that "clofibrate . . . should therefore be given for at least a year before it is assumed that a patient is unresponsive" because it may operate over many months before large tissue pools are reduced. I believe this sentence could be misleading. It would be a remarkable principle of therapeutics to continue a drug for a year before assuming that a patient is unresponsive. Your expert may have encountered one or two examples of very late response of serum lipids in patients with xanthomatosis, but

they are not well documented in the literature.

I suspect your expert made his directions too brief. In recent American journal advertisements (which contain three pages of text and 12 references) the manufacturers¹ advise as follows: "Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be made during the first few months of clofibrate administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, treatment should be continued for longer periods (even up to one year) provided there is reduction in the size of the xanthomata".

It is not quite correct, either, to say that there are no contraindications to its use. A paradoxical elevation of serum cholesterol has been reported in four patients with primary biliary cirrhosis when they were treated with clofibrate.² It would therefore be unwise to give the drug to patients with this type of secondary hypercholesterolaemia, in which tuberoses and palmar xanthomas can occur. The manufacturers advise that clofibrate should be given with care to patients with severe renal impairment and should not be given to patients with liver disease or pregnancy.—I am, etc.,

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¹ Advertisement on Atromid-S (clofibrate) by Ayerst, *Journal of the American Medical Association*, 1970, 214, 1230.

² Schaffner, F., *Gastroenterology*, 1969, 57, 253.

Renal Failure and Contrast Media

SIR,—We wish to reply to the comments of Dr. P. W. Robertson (23 January, p. 230) on our paper "Renal Failure after Radiological Contrast Media" (19 December, p. 717).

Case 1. Clearly Dr. Robertson would not have carried out aortography in this patient. We also feel that it was ill-advised but the advocates of high-dose procedures have so stressed the safety of contrast materials that some radiologists are now prepared to try it even in patients such as this. We fear that this situation will recur more frequently unless the risks are appreciated.

Case 2.—Like Dr. Robertson we also regard myelomatosis as a contraindication to contrast radiology, but this view is no longer universally held (3 April, p. 4). It has been claimed that modern contrast media are safe even in the presence of myeloma,¹ otherwise we should not have included this case.

We agree with Dr. Robertson that there is little "significant risk of renal failure following the orthodox use of contrast material." We were prompted to report these cases because of our concern as to where the limits of orthodoxy lie in this matter.—We are, etc.,

J. McEVoy
M. G. McGEOWN
R. KUMAR

¹ Lasser, E. C., Lang, J. H., and Zawadzki, Z. A., *Journal of the American Medical Association*, 1966, 198, 945.