of somewhat bizarre fibroadenomatous nodules in which it was difficult to differentiate the epithelial from the stromal component. There was some cell atypia and mitotic activity, but in both animals the nodules were well-circumscribed and showed no invasive tendencies. They thus appeared to represent early stages of the benign complex tumour of bitches as described by Conchin. A further observation was the occasional active epitheliosis with occasional mitotic figures in some of the ducts and acini in one of the animals, though there was no malignant change.

The appearance of fibroadenomatous nodules at a very early date in animals exposed to high dose levels of the natural hormone must, we believe, now give one serious cause to doubt the relevance to the human female of the development of similar nodules in animals given high doses of the derivatives of 17α-hydroxyprogesterone. This view is supported, moreover, by the lack of any real correspondence between the histological appearance of these nodules and mammary carcinoma in the human.—We are, etc.,

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Genetic Cripples

SIR,—Dr. N. J. Gross (17 April, p. 167) rightly criticizes Dr. G. Discombe’s estimates (23 March, p. 723) that raising the net reproductive rate (from, say, zero to unity) of patients with X-linked or autosomal recessive conditions will double the number affected in a generation. The doubling time is, as Dr. Gross indicates, a little under four generations for X-linked conditions and it is much longer for autosomal recessive conditions. Only autosomal dominants will double in one generation.

On the other hand, it is Dr. Discombe who is correct in sensing that the successful treatment of concentrated cases due to mutant genes of large effect poses a real dilemma. The birth frequency of such conditions is in the long run determined by the balance between the loss of mutant genes, from the lowered reproductive rate of the patients, and the gain of mutant genes, from fresh mutation. If improved treatments raise patients’ reproductive fitness, say, tenfold, and they choose to make full use of this, the birth frequency of the condition will in time rise to a new level. The ratio of benefit to risk in terms of offspring is in the end the same as if the patients had deteriorated in the same way, but with no treatment. The only point of difference is that the patients would come to resemble the general population, and then the case of the rarer disease will become even more complex.

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Penicillin Allergy

SIR,—In the Therapeutic Conference (3 April, p. 37) Dr. L. Stankler is quoted as saying that a rash "occurs in almost all patients with glandular fever who are given ampicillin." Presumably during the course of glandular fever the mechanisms responsible for the production of an allergic rash are modified in some way. It would be interesting to know if the nature of this modification was known, and also whether it is permanent. Furthermore, should it subsequently be assumed that the patient is allergic to ampicillin (and the other penicillins)?

Ampicillin is not infrequently prescribed for children and will subsequently turn to be a glandular fever. If the resulting rash is not due to a true permanent allergy, it may be that a very useful range of drugs is being withheld from a group of people in whom they could be used with safety.—I am, etc.,

T. PASTOR

Fibrinolytic Systems in Eclampsia

SIR,—The results reported by Dr. J. Bonnar and his colleagues (3 April, p. 12) lend support to the evidence that intravascular coagulation occurs in pre-eclampsia and eclampsia. In their discussion the authors
question the reasons for this, and it may be relevant that disordered coagulation has been described in both a mother and a baby following feo-maternal bleeding.

We have shown 1 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. 2 The placenta from 114 primiparae in this prospective study were examined, applying the method of Aherne and Dunnill for the assessment of macroscopic infarction, 1 and a statistically significant difference was found between the two groups (Table). We postulated that it was 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. 1 The hypercoagulable state of the woman in late pregnancy predisposes her to intravascular coagulation, and it seemed rational to suppose that the occurrence of partial anticoagulant release with the results that have now been described by Dr. Bonnar.

Incidence of Macroscopic Placental Infarction in 29 Hypertensive and 113 Normotensive Pregnancies

<table>
<thead>
<tr>
<th>Hypertensive Pregnancies</th>
<th>Normotensive Pregnancies</th>
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<tbody>
<tr>
<td>Placenta Infarcted</td>
<td>17</td>
</tr>
<tr>
<td>Placenta not Infarcted</td>
<td>11</td>
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</tbody>
</table>

Total 141; \( x^2 = 5.97 \); 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; thus 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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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 aspirin and paracetamol suggested 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 unmixed with other analgesics. As I have previously pointed out in your columns 1 and elsewhere, 2 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 Sari- don, 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 acetico-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 supposed 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 was 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—1 am, etc.,

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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 arteriography in this patient. We also feel that it was ill-advised but the advocates of high-dose procedures have stressed the safety of contrast materials that some radiologists are now prepared to try 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 myelomatisis 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, 2 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 publish our paper because of our concern as to where the limits of orthodoxy lie in this matter.—We are, etc.,

J. McEvoy
M. G. McGroW
R. Kumar