of somewhat bizarre fibroadenomatus 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. \(^2\) A further observation was the occurrence of 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 fibroadenomatus nodules only rarely occurs 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 rivotives 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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2 Conchin, E., Journal of Comparative Pathology and Therapeutics, 1958, 68, 1.

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Genetic Cripples

Sir,—Dr. N. J. Gross (17 April, p. 167) rightly criticizes Dr. G. Discombe's estimates (27 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 more in many 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 conditions 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 halve, unless things being equal, also rise tenfold. Then loss and gain are once again balanced. Whether the rate of increase be fast or slow, this constitutes a real problem in community health and Dr. Gross's personal view that we can do nothing about it is erroneous. Admittedly we cannot, in the foreseeable future, reduce mutation rates. But no increase whatever in birth frequency of these conditions will occur provided that patients do not make use of their increased fitness to have children. Further, in the case of X-linked and autosomal recessive conditions we may hope to do better still and in time to reduce the birth frequency well below the level maintained by the natural balance.

No authoritative dictum that haemophiliacs should not have children is required. Rather (as Dr. R. Biggs writes—10 April, p. 106) we should fully counsel patients and their relatives on the genetic risks to children and grandchildren and rely on their own good sense to plan their families accordingly. They must, of course, also (as she indicates) be given all necessary help to make their plans effective, including offering abortion and sterilization where appropriate. In one recent follow-up\(^1\) of patients given genetic counselling it was found that no couple planned further children after they had been told that there was a high risk of having a baby with haemophilia. On the other hand, some parents were prepared to take the risk of a condition from which the child would certainly die in infancy.

Just at present one would hope that few patients with severe X-linked conditions, including haemophilia, would plan children; but ethically the decision is and should remain theirs to make. However, it is to be expected that, with the help of fluorescent staining, techniques of X- and Y-bearing sperm will soon be developed. Well-treated haemophiliacs may then reasonably have as many sons as they wish, since these will be unaffected and have unaffected descendants. It would be much less reasonable for haemophiliacs to choose to have daughters since these must carry the gene. If they choose only sons there would be no rise in the birth frequency of haemophilia. Looking further ahead, the discovery of a simple means of detecting carrier girls will provide the opportunity of reducing the birth frequency well below the normal balance at zero reproductive fitness. The natural balance is at a birth frequency equal to three times the mutation rate. Two-thirds are born to carrier mothers, many of whom, if they knew the risk, would plan no children. Further, the discovery of ways of making early prenatal diagnosis of affected males and perhaps of carrier female fetuses, combined with the offer of abortion, would enable such women to have only unaffected sons and only daughters who were not carriers. Only the third of cases due to fresh mutations will therefore be found at the formidable undertaking of screening all pregnancies. The same techniques of carrier detection and prenatal diagnosis offer the prospect of the virtual elimination of autosomal recessive conditions, since in only a tiny fraction of these is a fresh mutation involved. Only for severe dominant conditions is there little prospect of reducing the birth frequency below the naturally balanced level.—I am, etc.,

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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 gonorrhoea, which subsequently turns out to be 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.,

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Prostaglandin-induced Labour

Sir,—We read with interest the article by Dr. G. Roberts and Professor A. C. Turnbull (27 March, p. 702), but lest prostaglandin, and uterine hyperactivity should somehow become linked in the mind of the reader we would like to emphasize two points in which this report of the use of prostaglandins for the induction of labour differs from previous reports.

Firstly, amnionotomy was performed prior to the infusion of the prostaglandin; this was uncommonly done in previous series.\(^3\) A recent double-blind trial of PGF\(_2\)E\(_2\) and oxytocin in the induction of labour we found it was often necessary to decrease the infusion rate of either drug after spontaneous membrane rupture to avoid uterine over-stimulation.\(^4\) This increased sensitivity of the uterus following membrane rupture may in part explain the hyperactivity reported by Dr. Roberts and Professor Turnbull.

Secondly, the doses used at the beginning of the infusion are far higher than usually used. Karim and Filshie\(^6\) have described the sudden increase in tone occurring in the mid-trimester uterus immediately following the infusion of 5 µg prostaglandin/min. We have not commonly seen this, even at that rate of administration, if low doses are used at the beginning of the infusion.

We agree with Dr. Roberts and Professor Turnbull that prostaglandins are powerful oxytocic drugs and endorse the view that great care is needed in their use, lest an undeserved, dangerous name be given to a group of drugs with enormous potential.—We are, etc.,

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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

\(^{1}\) F.D.C. Reports Inc., Washington D.C., 26 October, 1970, 22.
\(^{2}\) Conchin, E., Journal of Comparative Pathology and Therapeutics, 1958, 68, 1.
\(^{8}\) Gillespie, A., Beazley, J. M., and van Dorp, R. M., Clinical Genetics and Gynaecology of the British Commonwealth, in press.
question the reasons for this, and it may be relevant that disordered coagulation has been described in both a mother and a baby following foeto-maternal bleeding.

We have shown 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. The placenta from 114 primiparae in this prospective study were examined, applying the method of Aherne and Dunnill for the assessment of macroscopic infarction, 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 consequently coagulation within the placenta resulted in infarction. The hypercoagulable state of the woman in late pregnancy predisposes her to intravascular coagulation, and it seemed rational to suggest that this is of potential importance as a factor in fetal thromboplastin release with the results that have now been described by Dr. Bonnar.

### Chronic Phenacetin Nephropathy

Sir,—I strongly support the views and comments of Professor H. E. de Wardener and Dr. K. G. Kouaitamian (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 analgesics 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 unmixed with other analgesics.

As I have previously pointed out in your columns and elsewhere, 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 acet-4-chloranilide and its effective metabolite paracetamol. Paracetamol may eventually prove to be the agent responsible for the renal medullary damage, but this is not yet possible. If 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. —I 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 Radiocontrast 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 emphasized 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, 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 our case because of our concern as to where the limits of orthodoxy lie in this matter.—We are, etc.,