CORRESPONDENCE

Correspondents are asked to be brief

General Practitioners' Telephones

I. W. B. Grant, F.R.C.P.ED.	221
Candida and Dentures	
L. Forman, F.R.C.P.	221
Chlormadinone and Mammary Nodules	
D. K. Vallance, PH.D., and K. Capel-Edwards, B.SC.	221
Genetic Cripples	
C. O. Carter, F.R.C.P.	222
Prostaglandin-induced Labour	
A. Gillespie, F.R.C.S., and others	222
Penicillin Allergy	
T. Pastor, M.B.	222

Fibrinolytic Systems in Eclampsia

P. M. Jones, M.D.	222
Chronic Phenacetin Nephropathy	
N. G. Sanerkin, M.D., F.R.C.PATH.	223
Clofibrate	
A. S. Truswell, M.D.	223
Renal Failure and Contrast Media	
J. McEvoy, M.D., and others	223
Surgery for Rectal Prolapse	
R. S. Lawson, F.R.C.S.	224
Endocrine and Metabolic Disorders in Bronchial Carcinoma	
J. G. Azzopardi, M.D., and G. W. Poole, M.R.C.P.	224

Scarlet Fever

Sir John B. Cleland, M.D.	224
G.M.C.'s Functions and the B.M.A.	
R. Gibson, C.B.E., F.R.C.G.P.	225
G.M.C. Election	
W. S. S. Maclay, M.B.; M. R. Draper, B.A.	225
Keeping on the "Medical Register"	
Jean Lawrie, M.B.	225
Future of the Consultant Grade	
A. H. Grabham, F.R.C.S.	225
Female Medical Practice	
Agnes C. M. Vérel, M.B.	225
Tropical Diseases Unit, Edinburgh	
F. J. Wright, F.R.C.P.	225

General Practitioners' Telephones

SIR,—I should like to draw attention to the problems frequently encountered by consultants and other members of hospital staff when they try to telephone certain general practitioners in the evening or at weekends. On many occasions when I wish to obtain or provide urgent information about a patient, and dial the general practitioner's number, I am connected to the G.P.O. telephone exchange and told that the line is disconnected until the following morning, or even until the Monday morning, if I should happen to telephone on a Friday evening or a Saturday. I am then given the telephone number of the doctor who is on call for the practice, but he may know nothing about the patient, and unless the patient's own doctor has a second (ex-directory) telephone number which his colleague on call can give me I cannot get in touch with him even if he should happen to be at home. The prospects of doing so are reduced to nil if his calls are being diverted to an emergency treatment service, because no form of persuasion will induce the official in charge to divulge the general practitioner's ex-directory number.

This situation, I submit, can sometimes be extremely dangerous, since there are occasions on which information obtainable only from the general practitioner who has sent a patient into hospital may be of vital importance to his further management. Apart altogether from emergencies of this kind, there are many occasions on which I would

like to discuss less urgent clinical problems with a general practitioner and have not had the time or opportunity to do so during working hours, but my good intentions are only too often frustrated by a disconnected telephone. This unnecessary barrier is a source of considerable irritation to hospital consultants, and I have no doubt that it is a factor in limiting free communication between consultants and general practitioners.

It is always said that the purpose of omitting a general practitioner's home telephone number from the directory is to protect him from the demands of inconsiderate patients when he is off duty. There are, however, many doctors in Edinburgh, and no doubt elsewhere, who do not find it necessary to adopt this practice. I have spoken to many of these doctors (whom I am now apt to regard with a great deal more respect than the others), and they assure me that they are not, in fact, pestered by unnecessary calls from patients, provided of course that the on-call service through the surgery number is working normally. It is, therefore, difficult to understand why the practice of omitting home telephone numbers from the directory is so much on the increase, and I hope that this letter will cause my colleagues in general practice to ponder on its implications and consequences. —I am, etc.,

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Candida and Dentures

SIR,—The article on candida endocarditis treated with 5-fluorocytosine by Dr. C. O. Record and others (30 January, p. 262) prompts the suggestion that this hazard of candidal infection might be lessened if the *Candida* carried in the mouth by denture wearers (both in the patient and operating staff) is controlled before the operation is performed.

Candida albicans can be recovered from the dentures in from 30% to 70% of denture wearers, and in some of these individuals

there is evidence of active inflammation of the palate beneath the denture and of the palate posterior to the denture, and also of angular cheilitis. Careful cleansing of the denture, of the mouth and denture after each meal, removal of the dentures at night, and the use of nystatin or amphotericin B held in the mouth a week before the operation will clear the *Candida* from the mouth and the bowel.—I am, etc.,

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Chlormadinone and Mammary Nodules

SIR,—A little over a year ago the sales of oral contraceptive products containing chlormadinone acetate, a derivative of 17 α -hydroxyprogesterone, were suspended by the manufacturers because of the appearance of fibroadenomatous nodules in the mammary glands of bitches given very high doses (many times the human dose). In a leading article (31 January 1970, p. 252) you drew attention to the slender nature of the evidence which had brought the substance under suspicion, a view evidently shared by one of your correspondents (31 January 1970, p. 303). Nevertheless more recently a second derivative of 17 α -hydroxyprogesterone, namely medroxyprogesterone acetate, has been withdrawn from sale in the United States because of the appearance of similar nodules during the course of long-term toxicity studies.¹

In order, therefore, to place the situation in better perspective we would like to bring to your notice certain observations of our own made in pursuance of an extensive investigation (the results of which will be published in detail elsewhere) of the effects produced in beagle bitches by prolonged administration of high doses of the natural hormone. In this investigation progesterone was given by subcutaneous injection in an oily vehicle (90% v/v ethyl oleate, 7% v/v ethyl alcohol, 3% v/v benzyl alcohol) at three different dose levels, the animals in the highest dose group receiving 7.5 mg/kg/day for 24 weeks following an initial period of 12 weeks at 0.75 mg/kg/day, and then being given 22.5 mg/kg/day for a further 38 weeks. On completion of this 74-week period of treatment the animals were killed and a detailed postmortem examination carried out. Microscopic examination of the mammary glands (Professor W. B. Robertson and Dr. M. J. Davies, St. George's Hospital Medical School, London W.1) revealed marked lobular hyperplasia, mimicking pregnancy changes, in most of the treated animals, with secretory activity which was generally proportional to the dose of progesterone given. Sections from two of the five high dose animals, however, also indicated the presence

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 Cotchin.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 fibroadenomatous nodules at a relatively 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 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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1 F-D-C Reports Inc., Washington D.C., 26 October 1970, 22.

2 Cotchin, E., *Journal of Comparative Pathology and Therapeutics*, 1958, 68, 1.

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 than twenty generations for most 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 conditions will in time, other 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 authoritarian 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 offers of abortion and sterilization where appropriate. In one recent follow-up¹ 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 child with a severe persisting handicap. 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 for separating Y- and X-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 natural 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 male 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 then be inevitable, short of 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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¹ Carter, C. O., Roberts, J. A., Fraser, Evans, K. A., and Buck, A. R., *Lancet*, 1971, 1, 281.

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 hypertonus 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, amniotomy was performed prior to the infusion of the prostaglandin; this was uncommonly done in previous series.¹⁻³ In a recent double blind trial of PGE₂ 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 overstimulation.⁴ This increased sensitivity of the uterus following membrane rupture may in part explain the hypertonus 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 Filshie⁵ have described the sudden increase in tone occurring in the mid-trimester uterus immediately following the infusion of 5 μ g prostaglandin₂/min. We have not commonly seen this, even at that rate of administration, if low doses are used at the beginning of the infusion.⁶

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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1 Beazley, J. M., Dewhurst, C. J., and Gillespie, A., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, 77, 193.

2 Karim, S. M. M., Hillier, K., Trussell, R. R., Patel, R. C., and Tamusange, S., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, 77, 200.

3 Embrey, M. P., *British Medical Journal*, 1970, 2, 256.

4 Beazley, J. M., and Gillespie, A., *Lancet*, 1971, 1, 152.

5 Karim, S. M. M., and Filshie, G. M., *British Medical Journal*, 1970, 3, 198.

6 Gillespie, A., Beazley, J. M., and van Dorp, D. A., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, in press.

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 what 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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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