any new information. I read with interest that associations exist for such parents but this, to my mind, emphasizes the hunger for contact with others and the sense of loneliness felt.

Since the vast majority of cases occur in the home the collection, collation, and even computerization of this information must start from the parent. I am convinced that somewhere in the detailed case histories there are clues, but in the meantime innocent factors come under suspicion. I would not wish to belittle the valuable work already being done, but I believe a wealth of information is being neglected and the time has come for a drastic approach to this problem.—I am, etc.,

IRWIN PECK

Dry Drayton,
Cambs

Papillary Necrosis in a Transplanted Kidney

SIR,—The aetiology of renal papillary necrosis is a more complex problem than Dr. R. P. S. Edmonson and others (26 February, p. 547) appear to indicate. Histological changes, especially those recorded some time after the primary event, are not in general a reliable guide either to the cause of a lesion, or to the state of the blood flow at the time it occurred. Helderman and Klavins[1] considered that their in vitro experiments demonstrated the cytotoxic effects of complement activated human serum upon rat renal medulla; this had previously been shown in vivo.[2] In experimental renal papillary necrosis produced by ethylene imine[3] damage to all components of the medulla precedes demonstrable alterations in medullary blood flow. In this model we have now shown severe damage to all medullary cells within one hour of intravenous administration of the toxic compound.

It is only in the experimental model that the evolution of renal medullary necrosis can be studied in detailed sequence, and these indicate the existence of cytotoxic factors. Certainly, caution is needed in applying experimental observations to clinical conditions, but equal care needs to be exercised in postulating a common mechanism for the medullary lesions of sickle-cell anaemia and ureteric obstruction and the complete papillary necrosis complicating severe pyelonephritis, diabetes, and analgesic renal disease.—We are, etc.,

C. C. FUNDER
C. R. GREEN
K. M. HAM
J. D. TANGE

Department of Pathology,
University of Melbourne,
Victoria, Australia

1 Helderman, J. H., and Klavins, J. V., *Archives of Pathology*, 1970, **89**, 453.
2 Ljungqvist, A., Osvaldo-Decima, L., and Richardson, J., *Laboratory Investigation*, 1967, **17**, 447.
3 Ham, K. N., and Tange, J. D., *Australasian Annals of Medicine*, 1969, **18**, 199.

Pulmonary Oedema Related to Coronary Angiography

SIR,—Having encountered two cases of pulmonary oedema related to coronary angiography with left ventriculography I feel this should be considered a complication of the procedure. Your leading article (3 April 1971, p. 3) on "Hazards of Coronary Arteriography" lists the various hazards but does not include pulmonary oedema.

A 37-year-old white male had angina pectoris for two years with recent exacerbation but no history of cardiac decompensation. The E.C.G. showed transient ischaemic changes with pain. He was treated with nitroglycerin as needed and propranolol 20 mg orally four times daily, which he received till the evening before coronary angiography. A bilateral selective coronary angiogram by Judkin's technique was performed. Three injections each of 5-6 ml of 76% renografin were made into each coronary artery for three views. A left ventriculogram was made with the injector. His left ventricular end—diastolic pressure was 12-14 mm Hg before the ventriculogram, but after it rose to 22-25 mm Hg. Immediately after the procedure the patient developed cough and dyspnoea and became orthopnoeic. The situation was immediately recognized as left ventricular decompensation and treated with oxygen inhalation, frusemide 80 mg, and digoxin 0·5 mg given parenterally with good result. His coronary angiogram showed 70% obstruction of the main left coronary artery, 50% obstruction of the middle third of the posterior circumflex artery, and almost total obstruction of the right coronary artery. The left ventriculogram showed normal contractility.

The second patient was a 69-year-old male diabetic who had had angina pectoris for two years. During the investigation he became orthopnoeic and hypotensive and started to cough. Crepitations were heard in both lungs and accentuated pulmonary second sound. There was an improvement when oxygen, morphine, digoxin, and frusemide were administered, but he died the following day.

Necropsy confirmed the radiological finding of 70% stenosis of the main left trunk and the origin of anterior descending branch. The right coronary artery showed atherosclerosis without obstruction. There was severe pulmonary oedema. In both cases pulmonary oedema seems related to the procedure of coronary angiography/left ventriculography. It has been shown that left ventricular filling pressure rises during coronary angiography[1] and angiocardiography.[2] The degree of rise of left ventricular filling pressure is directly related to the severity of coronary artery disease. Contrast agents exert negative inotropic effects on myocardium, and this seems to be the most likely cause here. Propranolol might be another contributing factor by its negative inotropic effect.

It is concluded that any agent having a negative inotropic effect should be withheld as early as possible before coronary angiography and great caution is mandatory in patients who are suspected of having severe coronary artery disease on the basis of clinical evaluation. However, it is not possible to assess the severity of coronary artery disease in most cases without coronary angiogram and left ventriculogram. Monitoring of the left ventricular end diastolic pressure, at least in cases suspected of severe disease, may be worthwhile.—I am, etc.,

NAIYER HABIB

Columbus,
Ohio, U.S.A.

1 Gensini, G. G., Dubiel, J., Huntington, P. P., and Kelly, A. E., *American Journal of Cardiology*, 1971, **27**, 453.
2 Brown, A. K., Epstein, E. J., Coulshed, N., Clarke, J. M., and Doukas, N. G., *British Heart Journal*, 1969, **31**, 233.

Prostaglandins and Resistance to β-Adrenoceptor Stimulants

SIR,—We were most interested in Dr. Anne U. Tothill's suggestions (11 March, p. 689) that the release of prostaglandins may be particularly responsible for the resistance of human bronchial muscle to β-adrenoceptor stimulants, and that this resistance might be overcome by treatment with certain analgesics.

The effects of the prostaglandins on bronchial smooth muscle depend on the individual prostaglandins involved. Those of the E series relax bronchial muscle, and both prostaglandins E_1 and E_2 (PGE_1 and PGE_2) are bronchodilators in asthmatic subjects.[1,2] On the other hand, prostaglandins of the F series and particularly $PGF_{2\alpha}$ are potent bronchoconstrictors in a number of species, and in experiments in healthy male volunteers we have recently shown that the inhalation of $PGF_{2\alpha}$ results in an increase in airways resistance and a fall in specific airways conductance. In these circumstances the sensitivity of the bronchial muscle is not diminished; in fact, the inhalation of isoprenaline readily reverses the bronchoconstriction. On this evidence it therefore seems unlikely that prostaglandin release is responsible for resistance to β-adrenoceptor stimulants.

Although Vane[3] has demonstrated that aspirin and certain non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis, and Sweatman and Collier[4,5] find these agents effective in preventing the responses of isolated human bronchial muscle to $PGF_{2\alpha}$, we have been unable to demonstrate, in preliminary experiments, any suppression of the bronchoconstrictor action of inhaled $PGF_{2\alpha}$ in healthy volunteers previously treated with flufenamic acid, or any change in airways resistance in asthmatic subjects after ingestion of large doses of indomethacin. Indeed, some asthmatics may be adversely affected by treatment with analgesics and anti-inflammatory drugs[6] and we would not, at this stage, recommend this procedure.—We are, etc.,

A. P. SMITH

Chest Unit Department of Medicine,
King's College Hospital,
London S.E.5

M. F. CUTHBERT

Department of Pharmacology and Therapeutics,
London Hospital Medical College,
London E.1

1 Cuthbert, M. F., *British Medical Journal*, 1969, **4**, 723.
2 Cuthbert, M. F., *Proceedings of the Royal Society of Medicine*, 1971, **64**, 15.
3 Vane, J. R., *Nature New Biology*, 1971, **231**, 232.
4 Sweatman, W. J. F. and Collier H. O. J., *Nature (Lond)*, 1968, **217**, 69.
5 Collier, H. O. J., and Sweatman, W. J. F., *Nature (Lond)*, 1968, **219**, 864.
6 Smith, A. P., *British Medical Journal*, 1971, **2**, 494.

Reversible Airways Obstruction

SIR,—The paper by Dr. R. J. Alliott and others (26 February, p. 539) is of great interest to me as I have recently reported[1] a similar comparative trial of salbutamol and isoprenaline/phenylephrine with slightly differing results.

The patients I studied were 11 chronic bronchitics with reversibility of airways obstruction (increase in $FEV_1 \geqslant 20\%$ after bronchodilator). Baseline measurements were always made after the use of an aerosol containing inert propellant only, thus compensating for any placebo effect.

The Table shows mean changes (±S.E.) and probability values (*t* test) for FEV_1, $PaCO_2$, PaO_2, V_D/V_E, and cardiac output (Qt). Individual results were published in the previously mentioned paper.[1]

In contrast to the results of Dr. Alliott and others my patients showed a significant fall in Pa_{O_2} after salbutamol and a significant rise in Pa_{O_2} after isoprenaline/phenylephrine. FEV_1 response was identical with both aerosols, the dosage employed being salbutamol 200 μg, isoprenaline 320 μg, and 480 μg phenylephrine. Within the limitations of the indirect Fick C_{O_2} method, cardiac output appeared to be equally affected by both preparations (a probably insignificant rise). The rise in Pa_{O_2} after isoprenaline/phenylephrine was accompanied by a fall in Pa_{CO_2} and a reduction in V_D/V_E ratio. There was no evidence to suggest that the likelihood or degree of Pa_{O_2} fall with salbutamol was related to the baseline value.

It is difficult to know how much the inclusion of "pure" asthmatics in the series of Dr. Alliott and colleagues may have influenced the mean FEV_1 response. I would suggest, however, that chronic bronchitics with a significant degree of reversibility of airways obstruction may be more suitable subjects for this type of trial since they tend to remain stable with reproducible bronchodilator response between exacerbations. On the other hand "pure" asthmatics between attacks may not respond at all, although they are more likely to demonstrate the maximal effect of a given bronchodilator when on the upswing after an acute attack.

	Isoprenaline/ phenylephrine	Salbutamol
FEVI (litres)	+ 0·33 (± 0·05) P < 0·01	+ 0·32 (± 0·03) P < 0·01
Pa_{O_2} (mm Hg)	+ 4·72 (± 1·83) P < 0·05	− 4·0 (± 1·35) P < 0·02
Pa_{CO_2} (mm Hg)	− 3·8 (± 1·08) P < 0·01	− 1·1 (± 0·61) N.S.
V_D/V_E (%)	− 4·3 (± 1·27) P < 0·01	+ 0·3 (± 2·15) N.S.
Q_T (litres/min)	+ 0·93 (± 0·38)	+ 1·06 (± 0·53)

Mean changes (± S.E.) and P values

Both the results of Dr. Alliott and colleagues and my own suggest that both aerosols in the usual doses have relatively little effect on beta-1 adrenergic receptors. My results suggest that isoprenaline/phenylephrine improves the physiological state, and their results suggest that salbutamol may have a greater bronchodilator action. It should not be forgotten, however, that Professor Dollery's group has recently suggested[2] that the longer acting preparations such as salbutamol may be more likely to produce a state of resistance to beta-2 adrenergic stimulation.—I am, etc.,

LUKE HARRIS

East Chest Clinic,
Newsham General Hospital,
Liverpool

1 Harris, L. *Journal of Allergy and Clinical Immun.*, 1972, **49**, 63.
2 Connolly, M. E., Davies, D. S., Dollery, C. T., and George, C. F., *British Journal of Pharmacology*, 1971, **43**, 389.

Serum Transaminases and Salicylate Therapy

SIR,—In support of the interesting observations of Dr. A. S. Russell and others (22 May 1971, p. 428) I would like to present some further data about increased transaminase levels in children with rheumatic fever while on aspirin therapy.

After the accidental finding of high levels of glutamic-oxalacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) in two of our rheumatic fever patients on aspirin therapy, the salicylate level and liver function tests were closely followed in all similar patients and some previous records were also reviewed.

Rheumatic fever No. of patients	No. with raised transaminases	No. with salicylate level >30mg/100ml	Initial level SGOT units	Initial level SGPT units	Increased level SGOT units	Increased level SGPT units
14	10	9	10–40	5–27	51–300	47–275
Rheumatoid arthritis No. of patients						
3	2	2	15–23	5–26	170–200	165–225

Forty-one children fulfilled the modified Jones criteria for rheumatic fever and had SGOT and SGPT determinations at least at time of admittance to hospital. In no single case were these enzymes found to be raised at this time, and this was unrelated to the interval between the first clinical sign of disease and the determination of the transaminases. In eight children there were signs of active carditis but the transaminases were nevertheless normal. This is in contradiction to the observations of Nydick *et al.*[1] Twenty-nine of the 41 patients were treated with aspirin (90-120 mg/kg) but in only 14 children were the transaminases checked repeatedly together with salicylate levels. To this group three patients with juvenile rheumatoid arthritis have been added. The total of 17 patients thus represent all the aspirin treated children since 1969 when a possible relationship between this drug and raised transaminases was suspected.

It can be seen from the Table that the incidence of increased transaminases is rather high, but this, with one exception, is confined to those patients in whom the salicylate level was found to be higher than 30 mg/100 ml on at least one occasion. The earliest increase in serum enzymes was noted 10 days after institution of treatment, usually appearing two to three weeks after the aspirin was started. Increased transaminases were found so long as a high level of salicylate was present, the drop being very sharp (three to five days) after stopping treatment or reducing the aspirin dosage. These observations are in accord with previous reports on this subject.[1] Data on large series of aspirin-treated patients with transaminase determinations are still unavailable, possibly because the rise in transaminases is seldom accompanied by clinical or biochemical abnormalities. Only two of our patients had mild hepatomegaly; two had increased alkaline phosphatases, whereas serum bilirubin, prothrombin time, thymol turbidity, and Weltman reactions were normal in all patients. The bromsulphthalein excretion test was normal in the two patients on whom it was performed.

Acute hepatic dysfunction was recently reported in juvenile rheumatoid arthritis by Kornreich, Malouf, and Hanson[2] as an entity different to that described by Schaller, Beckwith, and Wedgwood.[3] In the light of the additional data here presented, it seems that salicylates, followed by gold compounds or indomethacin, may have played a much more important part in the induction of hepatic dysfunction in most of the cases reported by this group.

As an increased level of transaminases probably indicates cellular death, it would appear desirable that every child on aspirin therapy for rheumatic fever or rheumatoid arthritis should have these enzymes checked routinely together with the salicylate level. It is probable that a salicylate level of less than 30 mg/100 ml at any moment will keep the transaminases within the normal range.—I am, etc.,

THEODORE IANCU

Sharon Hospital and Tel Aviv University Medical School,
Petach-Tikva, Israel

1 Nydick, I., Tang, J., Stollerman, G. H., Wroblewski F., and LaDue, J. S., *Circulation*, 1955, **12**, 795.
2 Kornreich, H., Malouf, N. N., and Hanson, V., *Journal of Pediatrics*, 1971, **79**. 27.
3 Schaller, J., Beckwith, B., and Wedgwood, R. J., *Journal of Pediatrics*, 1970, **77**, 203.

Folate Deficiency and Anticonvulsant Drugs

SIR,—We were interested in the article by Dr. J. D. Maxwell and others (29 January, p. 297) suggesting that the folate deficiency occurring after administration of anticonvulsant drugs may be due to hepatic enzyme induction. In 1967-8 we estimated glutamate formiminotransferase and methylene tetrahydrofolate dehydrogenase, as well as serum and liver folates, in rats fed on or injected with phenobarbitone, diphenylhydantoin, or a mixture thereof. We showed[1] that the activity of both enzymes was usually increased.

Immature male or female Wistar albino rats were fed on a diet based on casein, with sucrose, lactose, fat, mineral salts, and vitamins added. In terms of the main types of nutrients, the diet provided 60% carbohydrate, 20% protein, 10% fat, 1% vitamins, and 9% mineral salts. Diets both deficient in and supplemented with folic acid (1 mg/kg diet) were used. In some experiments phenobarbitone (1, g/kg diet), diphenylhydantoin (1 g/kg), or a combination of both drugs (0·5 g each/kg) were added to the diet; in experiment No. 2 phenobarbitone (4 mg once or twice daily) was injected intraperitoneally into each animal. In all experiments control animals not receiving the drugs were maintained. The rats were killed between 5 and 29 days after starting the drugs and enzyme activities and folate were determined in the livers and folate was determined in the serum.

Glutamate formiminotransferase was determined as described elsewhere[2] and methylene tetrahydrofolate dehydrogenase was determined by the method of Kisliuk.[3] The determination of serum folate was by a modification of the method of Spray[4] and extracts of liver for the determination of hepatic folate were prepared by the method of Bennett, Berry, Chanarin, and Ardeman.[5]

The salient results are shown in the Table. Enzyme activities are expressed as units/100 g body weight because the drugs caused enlargement of the liver. In most experiments the drug-treated animals had significantly increased activities of both enzymes in the liver. Nevertheless, except for the serum folates in experiment No. 1 and the livers of the group treated with diphenylhydantoin in experiment No. 6, there were no significant differences in folate levels. It is possible that the experiments were terminated too early for such differences to be detected.