drugs. He is consequently able, on request, to advise the clinician on the selection of a drug, its most suitable form of presentation and dosage, and to warn him about side-effects and toxic reactions which may follow its use and the possibility of interactions with other drugs administered concurrently. Because of his training in pharmacology and his special interest in the therapeutic use of chemical substances, he is particularly well qualified to be a member of the team which is needed to prescribe and administer modern drugs in a rational manner.

The pharmacist is not an expert in therapeutics and cannot take the responsibility of prescribing drugs. Nevertheless, just as the doctor will place considerable reliance on the observations of nurses who watch the patient's condition carefully and on the findings of biochemists and bacteriologists who may not be medically qualified, so when writing his prescription he will attach considerable value to the advice of the pharmacist. The more clearly all these disciplines become welded into a closely knit team the better it will be for the patient. The pharmacist's special training also fits him to play a part in research involving studies of drug absorption and distribution in man, in the organization of clinical trials, and in drug-quality control.

Experiments are taking place in a number of hospitals at present in which the pharmacist visits the wards, examines all prescriptions, and makes himself available to medical and nursing staff to discuss with them the prescribing and administering of drugs. The Guild is following these experiments with great interest. It is hoped that in this way the integration of the pharmacist into the ward team may be brought about. It is a matter of great regret that adequate numbers of suitably experienced pharmacists are not available to enable these experiments to be carried out in many more hospitals.—I am, etc.,

G. RAINE,
Honorary General Secretary,
Guild of Public Pharmacists.

London W.C.1.

Biochemistry of Schizophrenia

SIR,—Your leading article (18 February, p. 382) says that "only some schizophrenics improve with phenothiazine treatment." While this may well be true, it cannot yet be regarded as a fact sufficiently well proved to be used as a starting point for new theories on the biochemistry of schizophrenia.

Possible sources of error are: failure to prescribe adequate and sustained dosage, failure to check that prescribed phenothiazines were actually taken, mistakes in the diagnosis of schizophrenia, observation of cases complicated by leucotomy, and observation of cases complicated by senility or arteriosclerosis.—I am, etc.,

Wellesley Hospital, Toronto, Canada. D. P. BIRKETT.

Compulsive Desire for Pregnancy

SIR,—Your leading article on "Sexual Promiscuity Among Students" (25 March, p. 711) is some of the best medical evidence yet published to demonstrate the foolishness of the social reasons proposed for abortion. The neurotic and, on occasions, compulsive

desire for pregnancy is so often suppressed temporarily in the social embarrassment of the pregnant state. On the advice of well wishers or in a gesture of conformity abortion is requested. If this request is granted severe and permanent damage may be done and the basic problem remain unsolved.—I am, etc.,

Welwyn Garden City,
Herts.

E. H. J. COTTER.

Haemodynamic Effects of Propranolol

SIR,—I was interested that Dr. Mary Stan-nard and Dr. J. G. Sloman (18 March, p. 700) found that in patients after acute myocardial infarction the fall in cardiac output caused by the intravenous administration of propranolol was prevented by the simultaneous administration of atropine sulphate.

Jose¹ has reported haemodynamic studies after intravenous injection of propranolol (0.2 mg./kg. bodyweight) and atropine (0.04 mg./kg.) to "isolate" the heart from the influence of parasympathetic and sympathetic nervous stimuli. In the normal subjects, isolation caused an increase in the heart rate, no change in cardiac output, and a rise in arterial pressure. Patients with myocardial disease showed a slower heart rate, higher end-diastolic left ventricular pressure, lower cardiac output, and lower arterial pressure than normal subjects. The measurement of heart rate alone after isolation paralleled as well as any other measurement the severity of myocardial disease assessed from clinical data. Jose has termed the heart rate after isolation with propranolol and atropine as "intrinsic heart rate" (I.H.R.). In normal adults aged 20 to 30 years he found that the I.H.R. averages 104 beats per minute. The I.H.R. declined progressively with increasing age. At ages between 45 to 55 years the I.H.R. averages 92, and at 70 years the average is 80. The I.H.R. is depressed in the presence of cardiac disease and appears to be a quantitative index of the severity of the disease. Serial measurements

may be useful in the assessment of the results of therapy. It is possible that I.H.R. estimation may be of value in diagnosis of subclinical coronary artery disease.

I have studied the I.H.R. in 61 patients with ischaemic heart disease and in 21 patients with hypertension. The I.H.R. was estimated after intravenous injection of 10 mg. propranolol and 2.4 mg. atropine. Pulse rate, blood pressure, and electrocardiogram were recorded before the administration and five minutes after blockade. In 26 of the patients with ischaemic heart disease (that is, 43%) the I.H.R. was lower than the estimated normal. One patient with an I.H.R. of 60 had refractory heart failure, and one patient with an I.H.R. of 56 had intractable angina. In six of the patients with hypertension (that is, 28%) the I.H.R. was lower than the estimated normal, and five of these six patients had evidence of hypertensive heart disease. The I.H.R. therefore appears to reflect myocardial function.

Of the 21 patients with hypertension, the I.H.R. was higher than the resting heart rate in 17 cases, and in no case was there a fall in the systemic blood pressure. Of the 61 patients with ischaemic heart disease the I.H.R. was higher than the resting heart rate in 50 cases, and in only three cases was the blood pressure lower after the intravenous propranolol and atropine. No significant side-effects were observed in any case. These findings support the conclusion of Drs. Stan-nard and Sloman that, if propranolol is indicated following myocardial infarction, it may be given with safety if combined with atropine sulphate.—I am, etc.,

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REFERENCE

¹ Jose, A. D., *Amer. J. Cardiol.*, 1966, 18, 476.

Deaths from Asthma

SIR,—In 1966 Smith¹ reported an increased death rate from asthma in England and Wales and this has been confirmed in the letter by Drs. R. Doll, F. Speizer, P. Heaf, and L. Strang (25 March, p. 756).

The figures shown below are from the Registrar General for Scotland. During the past three years there has been an increase in the number of deaths from asthma in Scotland and the decline in deaths from asthma noted in the fifties appears to have been reversed.

From Australia, McManis² has reported three deaths in asthma which appeared to have been due to cardiac arrest following the administration of adrenaline to patients who had already received isoprenaline. Following this there have been several reports which suggest a link between the excessive use of sympathomimetic amines and death in asthma (Greenberg³ and the recent letters

by Drs. M. J. Greenberg and A. Pines (4 March, p. 563) and Dr. W. Pickvance (25 March, p. 756)). This suggestion has been challenged by Herxheimer⁴ and Kennedy.⁵

The recently reported low arterial Po₂ tension found in some patients admitted to hospital with moderate or severe asthma⁶ has been confirmed in this unit. This observation, together with the changes in the electrocardiogram frequently found in these patients, suggests the myocardium is under strain. Some experimental work to support the concept that the myocardium when fatigued or under load is more susceptible to arrhythmias precipitated by isoprenaline has been reported by Professor Mary Lockett.⁷

Most of the sudden deaths in asthma occur out of hospital and the attention of the general practitioner must be directed to this problem. Meantime sympathomimetic amines should be avoided in the emergency

Number of Deaths from Asthma

Year:	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965
Male	109	116	106	93	76	56	61	59	83	55	82
Female	117	131	95	75	90	76	78	71	78	96	89
Total	226	247	201	168	166	132	139	130	161	151	171

treatment of asthma where there is a history of the excessive use of aerosol bronchodilators.—I am, etc.,

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- ³ Greenberg, M. J., *Lancet*, 1965, 2, 442.
- ⁴ Herxheimer, H., *ibid.*, 1965, 2, 298.
- ⁵ Kennedy, M. C. S., *ibid.*, 1964, 2, 689.
- ⁶ Tai, E., Read, J., *ibid.*, 1967, 1, 644.
- ⁷ Lockett, Mary F., *ibid.*, 1965, 2, 104.

Pressurized Aerosols in Asthma

SIR,—Recently correspondents have suggested that excessive amounts of sympathicomimetic drugs cause cardiac arrhythmias in asthmatics (4 March, p. 563, 25 March, p. 756). In this context I think the following case is of interest.

The patient, a man of 46, has suffered with asthma for 20 years. He was first admitted to this hospital in September 1966, with severe bronchial asthma and a pulse of 160 a minute. An electrocardiogram showed atrial flutter with 2:1 block.

The asthma responded to steroids. When free from bronchospasm sinus rhythm was restored with direct-current shock. He admitted to refilling his "Rybar" inhaler 10 times a day during the three days preceding this admission. This means he was inhaling approximately 200 mg. of adrenaline a day. When discharged he was advised to use inhalers sparingly. He was seen in outpatients a month later. There was considerable bronchospasm but he was in sinus rhythm.

He was readmitted on 2 March this year with a further attack of asthma. Again an electrocardiogram showed atrial flutter with a 2:1 block. In the week prior to admission he had used three "Bronchilator" inhalers—one in the preceding 24 hours (ten times the recommended maximum dose). Direct-current shock has again converted the flutter to sinus rhythm.

I thank Dr. R. D. Blachford for permission to publish this case.

—I am, etc.,

Selly Oak Hospital,
Birmingham.

P. D. EXON.

Traveller's Oedema

SIR,—During the recent flights of man in space, where gravity is non-existent, travellers' oedema was not observed, although the astronauts remained in the capsules up to 14 days.¹

The genesis of traveller's oedema is believed to be due to immobility and orthostasis. In the absence or reduction to a minimum of movements of the legs contractions of muscles which normally aid the flow of blood are non-existent, and a state of comparative venous stasis ensues. This is greatest in the lowest venules because of the greater hydrostatic pressure of the column of venous blood.² Thus oedema starts to form as soon as the lower extremities become inactive and continues to increase during the inactivity. It has been pointed out³ that the static filling pressure of the venous circulation in the vertical posture is chiefly determined by the size of the total blood volume of the venous

trunk and the potential capacity of the whole vascular bed.

Orthostasis is not a factor in the case of astronauts, since the hydrostatic pressure is nullified in the zero gravity environment. Regarding the factor of immobility, this is also neutralized owing to pneumatic cuffs used for massage of the legs and the programmed isometric muscular exercise performed by the astronauts.

Ideal conditions for a separate study of the immobility factor were expected to be present in experimental animals put in orbit round the earth. In effect, neither pneumatic cuffs to serve as a substitute of the muscle-pump nor any kind of muscular exercise imposed on the animals in space has been used in these experiments. Nevertheless, these animals, as seen in televised pictures, although apparently quiet, were alert and standing upright with their legs stretched.⁴ It is evident that the factor of immobility was absent in these cases too, and in a weightless environment, with the muscle-pump continuously working, the lack of hydrostatic pressure on the venous system facilitated fluid transfer from the extravascular spaces, thus preventing oedema.

It would be interesting to assess the effect of the immobility factor alone in the production of oedema in an animal kept under long-lasting anaesthesia during a long space flight.—I am, etc.,

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Greece.

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Treatment of Choriocarcinoma

SIR,—Professor W. S. H. Tow and Dr. W. C. Cheng's paper "Recent Trends in Treatment of Choriocarcinoma" (4 March, p. 521) touches the issue of how research into uncommon diseases can be effective. Before chemotherapy was applied to choriocarcinoma no clinician ever saw more than a few cases; there was no progress and the disease was almost invariably fatal. When a 23% recovery rate was reported¹ it became clear that cytotoxic chemotherapy had achieved its first major success, and gynaecologists quickly recognized the need for systematic studies. Treatment centres for choriocarcinoma evolved with the purpose of providing surgical, medical, nursing, and specialized investigatory facilities. In these units accumulated experience feeds back continuously into patient care, systematic evaluation of new therapeutic measures is facilitated, and knowledge gained from choriocarcinoma is applied to other neoplasia. Recovery of 70 to 80% of patients with trophoblastic neoplasias is now achieved, and, if diagnosed within four months of the antecedent pregnancy, is probably always curable. Much improvement in the treatment of cerebral metastases and advanced diseases is needed, however, and these improvements will probably come if systematic studies are maintained. If it were shown that the results of treatment in specialized centres were equalled by those in non-specialized units, the case for

specialized treatment would be weakened but not demolished.

Tow and Cheng write that they have safely and successfully managed the chemotherapy of choriocarcinoma with hysterectomy, fresh blood, and simple assays of human chorionic gonadotrophin. Modestly discounting the value of their own considerable experience, they suggest that other general gynaecological units can do the same for local cases. The reader is led to believe that some workers have claimed that hysterectomy is valueless and that sterile wards are essential. Such claims have not, I think, been made and they should not distract attention from the dissociation between Tow and Cheng's conclusions and their evidence.

The proposition that the Singapore results equal those obtained elsewhere should be based on sound comparisons. Tow and Cheng omit these, perhaps because their pathological classification, which admits hydatidiform mole and invasive mole into the category of "choriocarcinoma," precludes it. The least arbitrary basis for assessment of their results is the ratio of molar to non-molar pregnancies anteceding choriocarcinoma. Pre-chemotherapy studies^{2,3} found that for fatal cases this ratio was about 1:2. An epidemiological study found no evidence that mole was a relatively more frequent antecedent to choriocarcinoma in S.E. Asia than in the U.S.A.⁴ Most chemotherapy series include an excess of post-molar cases, but the Singapore series ratio is 4:1, and in the last 25 cases it is apparently 12.5:1. Accordingly, the expected number of fatal cases without treatment would be about 24. The reported figure of 30 deaths with treatment indicates either that the disease is different in Singapore or that treatment of potentially fatal disease there is ineffective. Despite the excess of benign lesions treated as choriocarcinoma, Tow and Cheng's fatality rate is twice that of a somewhat larger series at Fulham Hospital.

Hysterectomy is not valueless in choriocarcinoma, but Tow and Cheng do not do this problem justice. In Singapore more than three-quarters of the patients have more than three children;⁵ in our series a half are childless. Tow and Cheng do not hysterectomize young nulliparous women or those with widespread metastases; since no one has condemned hysterectomy in elderly multiparous women without evident metastases, all they are asserting is its value in patients with a few distant metastases. Their case for hysterectomy appears to be the belief, not any evidence, that it promotes spontaneous regression of metastases; the onus of proving such a case rests on its advocates, not its critics.

Tow and Cheng, advocating hysterectomy, write it "eliminates once and for all the source of tumour emboli and thus aids the body defence mechanism," and "its value has been amply demonstrated." This follows a discussion which explains why hysterectomy often delays appropriate treatment. They also compare a surgically fit hysterectomized group having a few metastases with a non-hysterectomized group which includes all their patients "with widespread metastases." The comparison is audacious, but the difference in results is not significant ($P = < 0.05$). The only clue to their conclusion lies in Table I of Tow⁶ and Table II of Tow and Cheng. Twenty-five recent additions to the series have included 12 further hydatidiform moles and no addition to the total number of deaths. Deaths in their "no chemotherapy" group have, however, increased and the total number of deaths in the "hysterectomy-chemotherapy" group have, by inference, decreased. Spontaneous resurrection? Or did the