feet still showed a large central necrotic zone with healing from the periphery proceeding very slowly (see Fig.).

Presumably, the ulcers on the left acromion and the left outer foot were directly related to the pressure of the full weight of the body. These lesions, however, do not appear to have been nearly as severe

as those on the opposing surfaces of the feet and knees where excessive sweating may have played an important role. It is well known that barbiturates are partly excreted in the sweat and there is a substantial literature quoted by Mandy and Ackerman¹ which shows that the maximum necrosis in barbiturate blistering is in the eccrine sweat epithelium. Beveridge² has stated that the eccrine sweat glands play a part in the formation of the blisters by excreting barbiturate, the concentration being increased by local blockage such as when two limbs or fingers are in contact. He points out that these are common sites of the bullae rather than the situations of maximal pressure.

The case here reported would tend to confirm that pressure plays some role in barbiturate blistering, but emphasizes that severe epidermal necrosis occurs particularly when pressure and excessive sweat concentration occur in conjunction with each other as in opposing surfaces of limbs which are in close and prolonged contact.

My thanks are due to the department of medical photography of the Oldham Hospitals Group for the photograph.

—I am, etc.,

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¹ Mandy, S., and Ackerman, A. B., *Journal of the American Medical Association*, 1970, 213, 253.

² Beveridge, G. W., *Archives of Dermatology*, 1970, 101, 369.

SIR,—You recently published my paper on Acute Poisoning: Some Myths and Misconceptions (6 March, p. 519), in which I drew attention to the ease with which the contents of articles inadequately supported by laboratory evidence might enter the mythology of acute poisoning. A plea was made to editors and their expert advisers not to publish articles where the sole evidence for the drug ingested was unconfirmed statements by patients or relatives. There could hardly be a better example of this uncritical approach than the paper "Bullous Lesions in Nitrazepam Overdosage" (3 July, p. 28). The title firmly states that bullae occur in nitrazepam overdosage, yet the evidence for in-

criminating nitrazepam and excluding barbiturates is no more than vague supposition and conjecture. No mention is made of any laboratory testing for nitrazepam or other drugs.

The only supporting evidence to the occurrence of bullae in nitrazepam overdose is given as "R. Goulding (personal communication 1970) at the Poisons Reference Service of Guy's Hospital." In December 1969 I had a communication from Dr. R. Goulding stating that bullae could occur in nitrazepam overdosage. Inquiry as to the validity of this information revealed that other substances might have contributed to the lesions attributed to nitrazepam.

It is not as if nitrazepam cannot be identified in the laboratory. Surely positive laboratory identification of nitrazepam, and negative evidence in the blood or urine regarding barbiturates, methaqualone, meprobamate, glutethimide, opiates, tricyclic antidepressants, and carbon monoxide should have been adduced to substantiate what can now remain but a myth.—I am, etc.,

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Smoking, Lung Cancer, and Asthma

SIR,—I would like to draw the attention of readers to the possible relationship between smoking, bronchogenic carcinoma, and asthma, because a preliminary survey of a large number of asthma sufferers has suggested some quite fascinating findings on this subject.

After suggestions that certain types of new growth seem to be less prevalent in patients suffering from allergic diseases, an analysis of over 25,000 allergic patients in Australia was started to try to confirm or otherwise this postulate. This group included some 13,000 asthma sufferers of all types seen over the past 12 years.

Every asthmatic at the first consultation is informed in no uncertain terms that he must give up smoking because of the sensitivity of his respiratory tract. Practically all follow this advice if it is put to them firmly enough; in any event most know from experience that they just cannot smoke without bringing on an attack of wheezing. The number of patients with this disease who are smokers therefore, even to a moderate degree, is quite small. Perhaps this is one reason why so few asthma sufferers, even those with severe recurrent disease over many years, develop destructive lung lesions such as emphysema, as opposed to the chronic bronchitic type of patient, who often uses the excuse that he must continue smoking in order to help him cough up sputum.

The main point of this letter, however, is to record the extraordinary fact that the results of observations so far on these 13,000 true asthma sufferers have shown that only one developed primary bronchogenic carcinoma over this 12-year period, and that was a man who had been informed some five years previously that he just had to give up smoking his 30-odd cigarettes a day, but he did not do so.

These findings suggest two possibilities. Firstly, that patients with asthma may have some resistance to the development of new growth, perhaps as a result of their hyper-

sensitive state, or secondly, that patients who do not smoke or give up smoking, even if they have chronic chest diseases, will not develop primary bronchial cancer.

It is hoped to publish the results of this survey in greater detail in the near future, relating them to the number of years each patient has been followed up, etc. It must be stressed at this stage that these findings are preliminary. They would appear to be so significant, however, that they should really be brought to the attention of the medical profession at this early stage because they suggest that further studies of this nature could well be carried out in different areas on an even wider basis.

This letter is largely written because I would be most interested to hear of the opinions of experiences on this subject of any physicians who have had wide experience in the care of bronchial asthma and lung cancer.—I am, etc.,

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Glutaraldehyde as a Bactericidal Agent

SIR.—Glutaraldehyde, a dialdehyde, is of particular importance in the field of hospital disinfection because, unlike most other commonly used disinfectants, it possesses sporicidal activity. It is used extensively as a chemosterilizer for endoscopes, anaesthetic equipment, and urological and other surgical instruments.¹ A stock 2% solution, when activated with 0.3% sodium bicarbonate, has a limited shelf-life of two weeks. This deterioration in bactericidal activity is thought to be the result of aldehyde polymerization at alkaline pH, the monomer being considered as being the active form.²

Recently, in the course of our studies³ into the nature of the antibacterial action of this dialdehyde against washed suspensions of *Escherichia coli* N.C.T.C. 9001, it was necessary to use different grades of glutaraldehyde obtained from different sources. These grades were: Kodak (25% solution), Koch-Light (25%), Cidex (2%), Polaron (8%) and Sigma (50%). Kodak and Koch-Light are commercial solutions of general industrial application, Cidex is the chemosterilizer used in hospitals, Polaron is a vacuum-distilled preparation containing a high amount of the monomer, and the Sigma preparation is stored over barium carbonate to prevent polymerization. Each was diluted to a concentration of 0.01%, sodium bicarbonate added to give a concentration of 0.3%, and *E. coli* incorporated to give an initial count of 3×10^6 viable cells/ml. Samples were removed at intervals during subsequent incubation for 1 hour at room temperature and viable counts made by the pour-plate method; colonies were counted after incubation of the plates for 48 hours at 37°C.

Of the glutaraldehyde samples tested, the Kodak solution produced a complete kill after 10 minutes, Cidex and Koch-Light after 20 minutes, and Sigma after 30 minutes, whereas with the highly purified Polaron sample complete loss of viability was not produced even after a 40-minute contact period. The samples containing the largest amounts of polymeric glutaraldehyde are thus more bactericidal than the samples containing a higher proportion of the monomer.

Although these results refer to one organism only it is apparent that in order to improve the bactericidal efficiency and shelf

life of this important chemosterilizer, investigations should be undertaken with the polymeric,⁴ rather than the monomeric, form of glutaraldehyde.

Full details of this work will be published elsewhere.—We are, etc.,

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- 1 Snyder, R. W., and Cheadle, E. L., *American Journal of Hospital Pharmacy*, 1965, 22, 321.
- 2 Stonehill, A. A., Krop, S., and Borick, P. M., *American Journal of Hospital Pharmacy*, 1963, 20, 458.
- 3 Munton, T. J. and Russell, A. D., *Journal of Applied Bacteriology*, 1970, 33, 410.
- 4 Richards, F. M., and Knowles, J. R., *Journal of Molecular Biology*, 1968, 37, 231.

Abdominal Swelling

SIR,—Mr. Wallace Barr (26 June, p. 758) has presented an excellent survey of abdominal swelling. May I be allowed to add three more conditions?

Hirschsprung's disease, in infants, gives a most characteristic almost quadrangular distension of the abdomen, roughly following the contours of the colon.

In rare instances polycystic kidneys may attain a size exceeding 10 kg for each kidney. In such cases a most pronounced abdominal swelling may be seen, dominant in the upper part of the abdomen "as if the patient had swallowed a chest of drawers."

What the Americans call "bloating" has been demonstrated to represent a special type of equivalent to migraine. It is characteristic that the distension may appear rapidly, most usually in the week preceding the period, and when the patient is for some reason tired. The mechanism has been dealt with elsewhere.¹ The distension may be so considerable as to masquerade as an advanced pregnancy (although confined to a few days). This syndrome is by no means uncommon.—I am, etc.,

ERIK ASK-UPMARK

Sweden

- 1 Ask-Upmark, E., and Frantzell, A., *Acta Radiologica*, 1950, 33, 104.

Morphine and the Fetal Heart Rate

SIR,—Increasing attention is being paid to measuring the fetal heart rate especially by monitoring, in order to minimize the development of asphyxia during labour. In particular, correlations have been found to exist between changes in the heart rate and the fetal pH and Apgar score of the infant at birth.^{1,2} These findings, while adding significantly to our management of at risk pregnancies, have not taken into account any effect that analgesics given to the mother during labour may have on the fetal heart rate. That morphine administered to the mother may result in a change in the fetal heart rate is illustrated by the following study.

The fetal heart rate was recorded in six antenatal patients at term for one hour by a Hewlett-Packard Cardiograph (8020A), and the mean baseline heart rate was estimated in each patient by averaging the rate observed at five-minute intervals. Morphine sulphate, 0.2 mg/kg, was then

given to each patient by intramuscular injection and the heart rate was again measured in a similar manner beginning one hour following the injection. The mean fetal heart rate in the six patients studied was found to be significantly less ($P < 0.001$) after maternal administration of morphine, an average change of 17 beats per minute being noted (Table).

Case	Fetal Heart Rate		Difference X
	Before Morphine	After Morphine	
1	136	123	13
2	136	124	12
3	140	125	15
4	153	133	20
5	136	116	20
6	146	126	20
X	141	124	17

Student paired 't' test.
 $t = 10.80 (> 6.87) p < 0.001$

It is not known whether these changes in the fetal heart rate in patients receiving morphine are due to an indirect maternal influence on the fetus, or to placental transfer which is known to occur. It is clear, however, that conclusions about the relation of the fetal heart rate to fetal wellbeing should in the future take note of prior drug therapy.—We are, etc.,

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- 1 Wood, C., Ferguson, R., Leeton, J., Newman, W., and Walker, A., *American Journal of Obstetrics and Gynecology*, 1967, 98, 62.
- 2 Wood, C., Newman, W., Lumley, J., and Hammond, J., *American Journal of Obstetrics and Gynecology*, 1969, 105, 942.

Testosterone for Anaemia in Maintenance Dialysis

SIR,—We have read with interest the paper by Dr. S. Shaldon and colleagues (24 July, p. 212) recommending the prolonged use of large doses of testosterone for the treatment of anaemia in patients on chronic intermittent haemodialysis. We have been unable to confirm his observations in four males on regular dialysis for a total of 30 hours a week over a period of one to four years who were treated with Sustanon [a proprietary preparation of testosterone esters]. Blood transfusions were not given and residual blood loss in the Kiil dialyser was negligible. Each patient was on a liberal protein diet and received intravenous iron supplements as required.

Three patients received intramuscular Sustanon 250 mg weekly for a minimum of nine months, and one patient received 250 mg weekly for four months and 100 mg weekly for three months. The initial packed cell volumes (P.C.V.) ranged from 17–22% and there was no significant rise in the P.V.C. in any of these patients. In one individual a steady fall occurred in the P.C.V. which rose again only after cessation of therapy. Because of these disappointing results we have not felt justified in treating more patients with androgens.

These findings suggest that further evaluation of this therapy is necessary before it can be recommended for general use in

patients on dialysis in view of the possible side effects of this dosage.

Dr. Shaldon states that there are many uncontrollable variables, and it may be relevant that folic acid and vitamin B₁₂ supplements are not given routinely to our patients but only when serum levels of these factors are low or there is other evidence of deficiency.—We are, etc.,

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Oat-cell Bronchial Carcinoma and Catecholamine Production

SIR,—The report by Dr. J. G. Azzopardi and others (28 November, p. 528) on the relation of histological and functional properties of bronchial carcinoma shows a surprisingly low incidence of Cushing's syndrome in their series. In several earlier reports a greater frequency of production of ACTH-like substance in bronchial tumours seemed to be evidenced or at least postulated.^{1,2} The warning of the authors—in other words the mistaken diagnosis based solely on hypokalaemic alkalosis—is fully justified.

We would like to add a new combination to the list of multiple hormonal secretion of oat-cell bronchial carcinomas so far reported.³ A 49-year-old man with bronchial carcinoma exhibited overt signs of Cushing's syndrome, but he also had frequent hypertonic crises with palpitation and sweating, giving a somewhat different picture from the usual. Two days after admission the patient died in a hypertonic crisis, and laboratory confirmation of the assumed multiple hormonal production in the tumour could not be confirmed (except the low serum potassium content—2.5 mEq/l.). Necropsy showed an oat-cell bronchial carcinoma, weighing 170 g, and bilateral adrenocortical hyperplasia (the weight of both the organs was 50 g. The adrenal cortex had several whitish-yellow nodules on it. Histological examination proved the nodules to be multiple adenomas composed of cells of the zona fasciculata with great foamy lipid granules. No change whatever could be detected in the pituitary.

Extraction of the tumorous material yielded an ACTH activity of 250 mU/g. In the gel electrophoresis of the substance eight to ten peptide components could be observed; one of them had the same motility as natural porcine and synthetic human ACTH.³ These data make it appear likely that the peptides were identical or at least analogous with ACTH. The tumour tissue also contained 12,750 µg/catecholamines, while the whole adrenals contained 120 µg of them. The bronchial tumour had a serotonin content of 576 µg, which is the maximal serotonin concentration ever reported except in the case of Smith.⁴

To our knowledge this case would be the first instance of non-endocrine tissue tumour producing non-polypeptide hormone (the serotonin can be considered more as a degradation product⁵). The event could be ascribed, however, to hormonal secretion of dispersed chromaffin or argentaffin cells in the bronchial tumour, though the most thorough histological examination failed to detect them.