Dangers of the Woulfe Bottle

SIR,—I was interested to read the article by Dr. B. J. Freedman on the value of the Woulfe bottle for the humidification of oxygen (29 July, p. 277).

In the course of time the water in these bottles can, and often does, turn into a culture of *Pseudomonas aeruginosa*. Experiments with a slit-sampler show that organisms are carried over from the bottles in oxygen bubbled through the water.

It is important, therefore, that such bottles should be washed out and sterilized at frequent intervals. The risk of contamination would be greatly reduced if, in addition, the bottles could be kept empty and dry when not in use, and water put in only when a patient needed to be given oxygen for more than a short period.—I am, etc.,

Department of Pathology, Royal Infirmary, Bradford, Yorks. W. M. EDGAR.

Friction is the Rub

SIR,—May I be permitted to voice a brief protest against the term "friction rub," which over the past few years has crept into the medical literature and has now achieved the distinction of appearing on the first page of the *British Medical Journal* in an otherwise most excellent leading article on "Chest Pain after Infarction" (5 August, p. 321). "Friction" and "rub" are each defined in terms of the other by all English dictionaries. Perhaps we shall soon be reading of murmur bruits and crepitation râles.—I am, etc.,

Wolverhampton. J. V. S. A. DAVIES.

Investigating Hypertension

SIR,—There is certainly need for balance in the investigation of hypertension, and I write to support the author of your leading article (1 July, p. 4). We have had a particular interest in hypertension and its investigation for twenty years, and two clinics each week are run for the management of patients undergoing long-term treatment with potent drugs. Almost all are first admitted to hospital for assessment to ensure that such a heavy life sentence is really necessary. It must be exceedingly uncommon for any potentially remediable surgical condition not to be suggested by a good intravenous pyelogram and isotope renogram, and, if significant, further investigation would be indicated by failure to respond to medical treatment. I think there may be a tendency for those with a particular interest in the surgical treatment of renal hypertension not to persist with antihypertensive drugs in appropriate combination with or without salt restriction, because our experience has been that treatment, if relatively difficult, is usually satisfactory in such cases.

The detailed investigation of 1,000 cases by aortography is impressive (Wing-Commander P. W. Robertson, 29 July, p. 306), but presumably they were mainly undertaken in relatively young, otherwise well, males.

I am sure that such a programme is justified for pure research, particularly if there is a possibility that the conclusion will be reached that such elaborate investigations are not necessary in most cases, but from the practical point of view of ordinary investigation I think that aortography is rarely required. Undoubtedly, of course, the larger the number of such investigations the more frequently will anomalies be found, but it does not follow that surgical treatment is indicated. It would be of great interest to know how many patients in this series were actually treated surgically and followed for, say, at least two years.—I am, etc.,

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Diabetic Lipaemia

SIR,—The occurrence of diabetic lipaemia (milky plasma) was first described in the nineteenth century and remains a well-recognized but rare manifestation of uncontrolled diabetes mellitus.[1] Although prompt diagnosis and insulin treatment of diabetes mellitus have probably reduced the incidence of diabetic hyperlipaemia, reports of the condition still occur.[1,2] I wish to record a case of massive hyperlipaemia in a young diabetic who was thought to be reasonably well controlled with insulin therapy.

A 13-year-old boy was admitted to the Royal Devon and Exeter Hospital complaining of vomiting and severe abdominal pain for 24 hours. The boy was known to be a diabetic for three years before admission and was usually well controlled on 24 units lente insulin daily. On examination he had a tense abdomen but no masses were palpable. It was noted that he had a rapid respiratory rate and extreme difficulty in breathing. The white blood count was 30,000 cells/cu. mm., of which 83% were neutrophils. The blood sugar was 176 mg./100 ml., serum amylase was 160 Somogyi units/100 ml., serum sodium was 111 mEq/l., serum potassium was 3.1 mEq/l., serum chloride was 70 mEq/l., and bicarbonate 18 mEq/l. The serum was noted as being extremely milky in appearance. The urine contained glucose and a moderate amount of acetone.

Because of the uncertain diagnosis, laparotomy (Mr. C. Shaldon) was undertaken. At operation the stomach, jejunum, and bladder were dilated, but no cause was seen to account for these findings. A striking feature at laparotomy was the pink creamy consistency of the blood. After operation he was given 20 units soluble insulin three times daily and improved rapidly. Although the blood sugar was never apparently greater than 250 mg./100 ml., acetonuria persisted for a few days. After operation lipaemia retinalis was observed, but there were no microaneurysms or xanthomata. The plasma lipids were analysed on a preoperative specimen and on succeeding days. The results (Table) show a gross hyperlipaemia which gradually cleared. Since this time the boy has remained well and is receiving 36 units soluble insulin and 12 units protamine zinc insulin daily. Examination of the patient's parent's plasma has not shown any increase in the lipid content.

Day	Cholesterol (mg./100 ml.)	Total Serum Lipids (g./100 ml.)	Lipoprotein
0	1,350	14·9	Chylomicrons
3	508	3·4	Pre-β
5	540	2·4	β
6	490	1·76	β
9	—	1·14	—
19	—	1·56	—
3 months	186	0·9	β
6 „	113	0·6	—

Normal range—140–265 mg./100 ml. 0·34–0·9 g./100 ml.

The occurrence of massive hyperlipaemia in diabetes mellitus is described as a rare syndrome,[2] but was a more frequent observation in the era before insulin treatment of diabetes.[3] This case is unusual in that the boy had been well until 24 hours before admission, whereas other cases described have been preceded by a long period of illness.[1] It is probable that diabetic hyperlipaemia is an acquired but reversible form of fat-induced hyperlipaemia with subnormal post-heparin lipolytic activity and delayed removal of dietary fat.[1] The decreased activity of the enzyme appears to be secondary to hormone deficiency, which results in impaired synthesis of the enzyme in contrast to the inherited defect in enzyme synthesis seen in the familial disorder.

I should like to thank Dr. L. Haas and Mr. C. Shaldon, under whose care this patient was admitted, for permission to report this case.

—I am, etc.,

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REFERENCES
1 Bagade, J. D., Porte, D., jun., and Bierman, E. L., *New Engl. J. Med.*, 1967, **276**, 427.
2 Mune, O., and Nørregaard, S., *Dan. med. Bull.*, 1966, **13**, 198.
3 Joslin, E. P., Root, H. F., White, P., and Marble, A., *The Treatment of Diabetes Mellitus*, 10th ed., 1959. London.

Carcinogenic Properties of Ortho-dianisidine

SIR,—Dr. H. Lehmann's letter (19 August, p. 494) about the carcinogenic properties of ortho-tolidine (3:3′-dimethylbenzidine) and ortho-dianisidine (3:3′-dimethoxybenzidine) and his lament that in your leading article (22 July, p. 189) you do not give firm advice about whether these substances should be used or not in clinical routine practice raises an important question which at the moment cannot be answered in a simple and definite manner.

The Chester Beatty Research Institute has been asked from time to time to give guidance on this matter to individuals. The advice that has been given is as follows: While we believe that it is possible to handle these substances safely if adequate[1] precautions are taken, we think that suitable alternative methods should be sought, for sooner or later laboratory workers may become careless, and the dangerous substances must be manufactured, purified, and packed, possibly exposing other workers to a hazard.

Whether alternative techniques are satisfactory or not can often be assessed only in the framework of the duties of the laboratory concerned. However, the Association of Clinical Pathologists has already taken the initiative, and in a circular to its members[2] has asked biochemists who know of suitable alternative methods, particularly for techniques for the estimation of glucose by the glucose-oxidase method, to let the Association know. The leaflet gives a reference[3] to a bibliography of possibly useful tests for occult blood which are not based on carcinogens.

Some workers have informed me that they have changed to alternative techniques for glucose estimation—specific for glucose and

not merely the estimation of reducing substances—which meet the needs of their particular laboratories.[4–6] Perhaps it would be helpful if details of their experiences with these methods were made available to biochemists, either through your columns or through the Association of Clinical Biochemists.

Similar problems have arisen in relation to the use of ortho-tolidine in tests for residual chlorine in water—in this case the Water Research Association has recommended an alternative test based on NN'diethylparaphenylene diamine, which is not believed to be carcinogenic—and in relation to the use of 1-naphthylamine in tests for nitrates in sewage effluents or in urine. Recently an alternative test for urinary nitrites has been proposed.[7] Here again it would be useful if the experience of those who have changed to alternative methods could be collated and brought to the notice of biochemists.

Since it is apparent that it will not be possible to abandon the use of all carcinogenic aromatic amines in medical biochemistry immediately, it would be wise in the meanwhile for the head of every laboratory where these substances are used to ensure that all his staff are aware of the possible dangers and of the necessary precautions, and to see that these precautions are in fact observed. —I am, etc.,

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REFERENCES
1 Chester Beatty Research Institute and Harlow Industrial Health Service, *Precautions for Laboratory Workers who Handle Carcinogenic Aromatic Amines*, 1966. London.
2 *Association of Clinical Biochemists*, 1967, News Sheet, No. 53, July, p. 2.
3 Henry, R. J., *Clinical Chemistry Principles and Technics*, 1964. New York.
4 Kelly, D. M., *Clin. Chem.*, 1965, **11**, 471.
5 Brown, M. E., *Diabetes* 1961, **10**, 60.
6 Bittner, D. L., and McCleary, M. L., *Amer. J. clin. Path.*, 1963, **40**, 423.
7 McLean, J., and Henderson, A., *J. clin. Path.*, 1966, **19**, 632.

Transplacental Transmission of Herpes Simplex

SIR,—Gregg in 1941[1] and Swan and his associates[2] in 1943 first reported clinical observations on congenital anomalies in the offspring following maternal rubella. While Swan's observations were concerned chiefly with rubella, he postulated that other virus diseases in the mother might result in foetal maldevelopment.

Herpes simplex infection of the newborn may occur by transplacental transmission of the virus as well as by the more common mode of infection from active lesions in the birth canal.[3] Between 65% and 98% of adults will show neutralizing antibodies to the herpes simplex virus.[3] The incidence of herpetic lesion in the female genital tract is greater than generally recognized. Naib *et al.*[4] found that of approximately 40,000 indigent patients screened for cancer by routine "Pap" smear 62 (0.16%) had initial cytological evidence of a herpetic lesion. About one-third of these were pregnant. Because of these facts and because of the fact that herpes simplex virus in tissue culture causes a high percentage of chromosome aberrations,[5] it is plausible to suggest that herpes simplex cervicitis during early pregnancy may cause congenital malformations.

A 22-year-old primipara was admitted to the department of obstetrics and gynaecology at the General Hospital, Malmö, Sweden, on 23 June 1966 in labour. During the third month of pregnancy she was first seen in the outpatient service. At that time the labia majora were noticed to have several small ulcerations. The routine "Pap" smear showed initial cytological evidence of a herpetic lesion. The ulcerations healed spontaneously, and the pregnancy was uneventful until the 36th week of gestation, when the patient underwent a caesarean section because of toxaemia. The child was a phocomelus and died some hours after delivery because of respiratory distress. As far as we know the patient had not taken any medication during her pregnancy. From the age of 8 years she had been treated with insulin because of diabetes mellitus, which may give malformations, but as far as is known not of this kind.

The present congenital malformations and the maternal herpes simplex infection during early pregnancy may be coincidental. As no studies of a relationship appear to have been published, we hope that others may follow up cases with cytological evidence of herpetic lesions during early pregnancy, and report cases of foetal maldevelopment if any appear. —We are, etc.,

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REFERENCES
1 Gregg, N. McAlister, *Trans. ophthal. Soc. Aust.*, 1941, **3**, 35.
2 Swan, C., Tostevin, A. L., Moore, B., Mayo, H., Blach, G. H. B., *Med. J. Aust.*, 1943, **2**, 201.
3 Mitchell, J. E., McCall, F. C., *Amer. J. Dis. Child.*, 1963, **106**, 207.
4 Naib, Z. M., Nahmias, A. J., Josey, W. E., *Cancer (Philad.)*, 1966, **19**, 1026.
5 Stich, H. F., Hsu, T. C., Rapp, F., *Virology*, 1964, **22**, 439.

Snakebite Poisoning

SIR,—Dr. H. A. Reid (5 August, p. 367) has drawn attention to a newspaper report of snakebite which occurred in a local man.

At the time some concern was caused by the presence of local pain and tenderness, and of dilated pupils and weakness apparently not caused by fear alone, following injury by an unusual snake. This was later identified as a European grass-snake. For the future we have learned from the incident that antivenom is kept in the zoo concerned.

Needless to say, the drama of the occasion was considerably less than was depicted in the press.—I am, etc.,

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Ehlers-Danlos Syndrome

SIR,—Ehlers–Danlos syndrome may have a wide variety of manifestations. It is often difficult to be sure of the diagnosis, particularly in mildly affected individuals, since the microscopic anatomy is in "a disputed state," and the basic defect is unknown.[1] Thus Mr. A. P. Barabas's suggested clinical subdivision of cases (3 June, p. 612) is most helpful in elucidating the probable heterogeneity of the syndrome, and particularly in pointing out the existence of an "arterial" type which may cause fatal haemorrhage in early adult life.

As Mr. Barabas is aware, intracranial arterial aneurysm has been reported as a complication,[2] and one of us recently described three cases of spontaneous carotid-cavernous fistula in Ehlers–Danlos syndrome.[3] Two of the patients are siblings, a sister and brother, and the sister has since died after suffering a succession of further arterial complications. A brief report of this case may therefore be of interest.

She was last seen in 1961, aged 37, with a spontaneous left carotid cavernous fistula associated with remarkable ectasia of the left internal carotid artery, and alarming haemorrhage occurred at the time of carotid arteriography. Carotid ligation was performed, and one month after operation she developed small aneurysms of the left radial artery and the left superficial temporal artery. The latter disappeared spontaneously. These episodes and further complications occurring up to 1964 have been reported.[3] Her previous history included lifelong easy bruising and a myocardial infarction at the age of 35.

In 1965 she still had an aneurysm of the left radial artery, which was later excised at another hospital. In April 1967 the patient complained of weakness, fatigue, and fever, and then developed severe right-sided headache and blurring of vision in the right eye. On admission to hospital she showed right proptosis and third-nerve palsy, suggesting a right internal carotid aneurysm. Angiography was deferred because of the previous experience and because she also had many features of a systemic disease resembling polyarteritis nodosa. These included fever, hypertension, chest pain, weakness and extreme tenderness of limb muscles, leucocytosis, normochromic anaemia, and a very high sedimentation rate. Skin and muscle biopsy proved inconclusive, showing only slight perivascular infiltration, but a disturbance in the pattern of elastic fibres, in some parts loose and in others arranged in compact masses with a tendency to form nodules, was noted, compatible with the diagnosis of Ehlers-Danlos syndrome (Dr. Mario Montes).

She was treated with corticosteroids, and subjective improvement and disappearance of fever followed; vision improved in the right eye, and the proptosis and right third-nerve lesion both regressed. However, chest pain recurred and electrocardiographic evidence of a further anterior myocardial infarction was seen. Subsequently, a further aneurysm appeared on the right radial artery, the mirror image of that earlier excised on the left. Soon after, she suffered sudden acute swelling in the left calf with agonizing throbbing pain. This was thought to represent rupture of another aneurysm, and at operation, reluctantly undertaken, a false aneurysm was found arising from the left posterior tibial artery. Some 10 days later another aneurysm appeared on the right anterior tibial artery. Finally the patient complained of acute abdominal pain and became unconscious. Blood was aspirated from the peritoneal cavity but there was no time to attempt operation before she died. Necropsy showed that she had ruptured an aneurysm of the splenic artery; other aneurysms were found on mesenteric arteries. Polycystic disease of the kidneys and liver was also found.

It seems worth emphasizing that this patient had thin and unusually smooth skin, but it was not redundant or hyperelastic, and her joints were not unusually lax. As noted previously,[3] her brother had a similar left-sided carotid-cavernous fistula at the age of 30, but we are not aware that he has ever had other arterial complications, although we have not yet had an opportunity to examine him. A full study of the family is in progress; there is no other positive evidence of Ehlers-Danlos syndrome, although there are