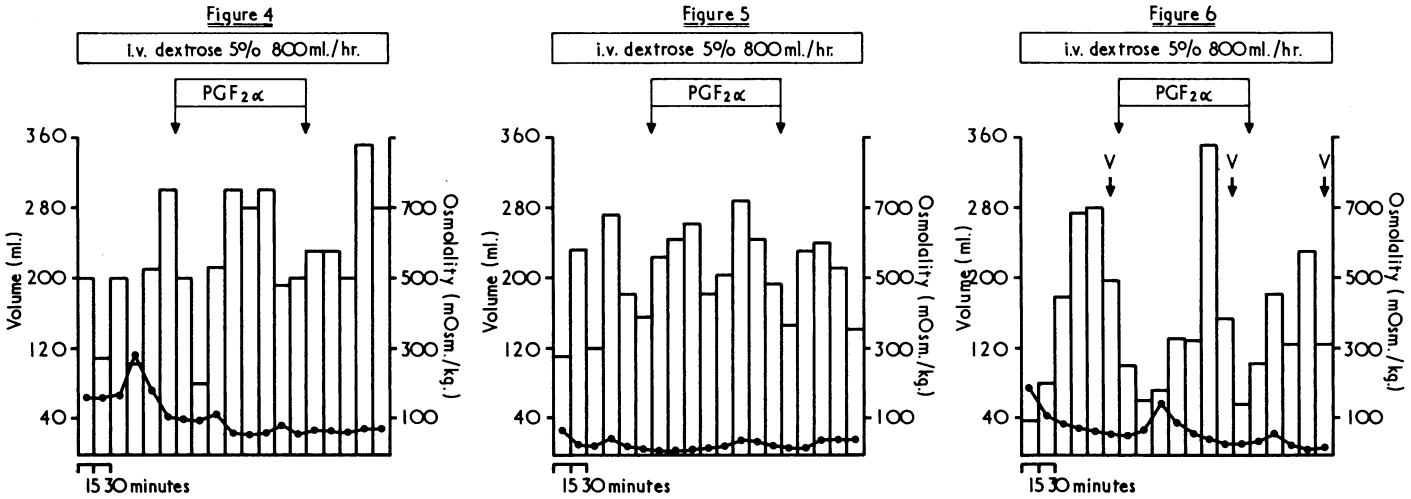

FIGS. 4, 5, and 6.—Lack of antidiuretic effect in response to intravenous $PGF_{2\alpha}$ infused at 0.05 μg./kg./min. The patients were being given a continuous intravenous water load (see text). Criteria represented as in Figs. 1-3. V = vomited.

pharmacological agent for the induction of labour, the absence of an antidiuretic effect would represent a significant advantage over oxytocin.

The risk of water intoxication with dilute solutions of oxytocin has been reported by Liggins (1962) and by Whalley and Pritchard (1963). If large doses of oxytocin are required to induce labour successfully, then the fluid intake should be limited and the *concentration* of oxytocin increased rather than the *rate* of infusion. One of us (G.R.) noted probable water intoxication in a patient who developed an "eclamptic fit" following administration for 14 hours of 3,600 ml. of 5% dextrose containing 8 units of oxytocin per litre. There was no hypertension or albuminuria, and the clinical picture was similar to that described as water intoxication by other workers. Presumably, the risk of such a complication would be much less with $PGF_2\alpha$. It may be of particular value when labour has to be induced because of pre-eclampsia or chronic renal disease, since renal function may be depressed, or in heart disease where plasma volume may be expanded to a dangerous level if an antidiuretic drug is used.

This work was carried out during the tenure of a United Cardiff Hospitals' Research Fellowship to one of us (G.R.). We wish to express our thanks to Professor van Dorp, Vlaardingen, for providing the prostaglandin and to Professor V. R. Pickles for helpful advice.

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Medical Memoranda

Severe Generalized Primary Herpes Treated with Cytarabine

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Cytarabine has been shown to be effective against a number of D.N.A. viruses in cell culture (Underwood, 1962; Underwood *et al.*, 1964), including vaccinia and herpes simplex virus. Kaufman and Maloney (1963) found that cytarabine in a 5% saline solution was as active as idoxuridine in the treatment of herpetic keratitis in 12 patients.

Toxic side-effects of the drug when given systemically in humans in the treatment of malignant disease in doses of 2-5 mg./kg./day include megaloblastosis and marrow suppression, including leucopenia, anaemia, and thrombocytopenia (Talley and Vaitkevicius, 1963).

Cytarabine has the great virtue of being water soluble, and in view of the favourable results in the treatment of herpetic keratitis and our own favourable though limited experience with the drug used locally in herpetic skin lesions it seemed reasonable to try the effect of cytarabine in a patient in whom a primary infection gave rise to concern.

CASE HISTORY

A 22-year-old male medical student presented on 28 October 1969 complaining of a sore throat and malaise. Apart from recurrent attacks of bronchitis during childhood and early adult life he had had no serious disease. He had never suffered from cold sores. From 22 to 25 October he had daily met and kissed a girl friend, who at that time was "fighting off a cold" and had had "sores on her

tongue." On examination he had a temperature of 99°F. (37·2°C.), a pulse of 70, the fauces were red and oedematous, and there was some cervical adenopathy, but no enlargement of the nodes elsewhere. The spleen was not felt and the liver was not enlarged. The following day he was ill, sweating, his temperature had risen to 102°F. (38·9°C.), and he had general aches and pains and headache. A few small lesions had developed on the left side of the soft palate and the adenopathy had become generalized.

Throat cultures taken on 28 October yielded no bacterial pathogens, but herpes simplex virus was isolated. As the complement fixation test (C.F.T.) to herpes simplex was <1/4, a diagnosis of primary herpetic stomatitis seemed certain. During the night of 29 October his general condition deteriorated. He became toxic and confused and had nightmares. On the morning of 30 October the adenopathy was more pronounced and the liver had become enlarged 2 cm. below the costal margin in the midclavicular line. The spleen was just palpable. He had several lesions on the soft palate and an ulcer on the inside of the lip. There was no neck stiffness, but the sensorium had become clouded. It was clear that he was very sick, with an attack of the primary infection much more severe than usual, and it was possible that the illness might become life-threatening. The possible use of chemotherapy was discussed with a virologist and a haematologist who had considerable experience with cytarabine in the treatment of leukaemia. It was felt justified to treat the patient with systemic cytarabine in a dose which was unlikely to cause major toxic effects. Cytarabine 0·3 mg./kg. (he weighed 64 kg.) was given intravenously once a day from midday on 30 October for five days, a total of 100 mg. Daily estimations of W.B.C., Hb, and platelets were done, together with serum alanine aminotransferase (S.G.P.T.), alkaline phosphatase, and urea estimation. Within 12 hours he was much improved, and within 18 hours the temperature had settled. The liver was enlarged by only 1 cm., and the spleen was not palpable. On 1 November his throat was no longer sore and the lesions had disappeared. The liver was of normal size and the lymph nodes were smaller. Herpes simplex virus was isolated daily up to and including 3 November, but daily swabs thereafter were negative up to 10 November, when they were stopped. Cytarabine was discontinued on 3 November. At no stage had the patient had any toxic side-effects from the treatment, and the subsequent course was completely uneventful. He was discharged on 7 November and has remained well.

The laboratory findings during treatment are shown in the Table. The blood uric acid on 5 November was 8·2 mg. and on 7 November 6·4 mg./100 ml. On 28 October a Monospot test was negative. The C.F.T. to herpes simplex was: 29 October <1/4, 10 November 1/128, and 26 November 1/32. Culture of the virus from the leucocytes of the patient's blood was attempted on 30 October. Final conclusions had not been reached at the time of this report, but the culture was probably negative.

Laboratory Findings during Treatment

	W.B.C.	Platelets	Hb (g./100 ml.)	S.G.P.T. (S.F. Units)	Urea (mg./100 ml.)
28/10/69	6,700	N.D.	14·9		
Cytarabine started 30/10/69	7,600	122,000	14·2	12	22
31/10/69	5,300	76,000	14·3	14	26
1/11/69	4,500	130,000	14·5		
Cytarabine stopped 3/11/69	4,700	120,000	14·4		
4/11/69	4,900	180,000	14·4		
5/11/69	6,600	170,000	14·5	28	28
6/11/69	5,000	164,000	14·2		
7/11/69	6,600	220,000	14·5		
26/11/69	Repeated counts to the present: normal figures			6	

S.F. = Sigma-Frankel.

The patient's girl friend was traced but not seen until 3 November. She gave no previous history of cold sores and her oral ulcers had healed. A swab was negative for herpes simplex, but a C.F.T. of 1/32 makes it possible that she had had primary herpetic stomatitis and had infected the patient.

Comment

Severe cases of generalized herpes infection are uncommon and usually occur in children; in adults they are rare. The disease may run a rapidly fatal course. Diderholm *et al.* (1969) described generalized herpes with stomatitis in a man of 60 with asthma who died within 12 days.

The rapid resolution of symptoms and signs without any obvious toxic effects from the treatment with cytarabine in the present case was encouraging. The slight depression of the W.B.C. and platelet counts may have been due to the drug, but could be explained by the infection itself. The transient rise of the serum alanine aminotransferase could likewise well have been due to the virus rather than the drug, for hepatocellular involvement is common in infections with members of the herpes virus group. The fairly dramatic improvement in the condition after the administration of cytarabine could have been a coincidence; against this is the very short period during which it was possible to isolate virus from the local lesion—that is, for only five days after treatment with cytarabine was begun, when usually in patients with primary herpetic stomatitis virus persists for weeks.

My thanks are due to Dr. F. O. MacCallum and Mr. Ivor Chinn, of the virology laboratory, to Dr. Pauline Emerson, of the haematology department, and to Dr. R. H. Wilkinson, of the biochemistry department of the Radcliffe Infirmary, for their help. I am grateful to Dr. Sögtrop, of Messrs. Heinrich Mack Nachf., for providing cytarabine for clinical trial.

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ADDENDUM: I have since treated a further five patients with cytarabine. Two had blast cell leukaemia and developed severe stomatitis (and one pneumonitis) while on immunosuppressive drugs. Another developed severe stomatitis while on high doses of steroids for an allergic disorder; a 27-year-old male had extremely severe eczema herpeticum and generalized herpes; and a man of 26 was thought to have early simian herpesvirus encephalitis. All made a dramatic recovery. Bigger doses of cytarabine, up to 2 mg./kg./day for five days, were used (this was the case in the very-ill young man with generalized herpes and eczema herpeticum), and it is of particular interest that although the white count dropped in the patients with leukaemia (one went into remission) in none of the patients with a normal bone marrow was there any detectable effect on W.B.C. and platelet counts or on the haemoglobin.