cancer, the ratio of etiocholanolone to 17-hydroxysteroids in urine (Bulbrook *et al.*, 1960), could be a non-specific effect of illness. Further, Russfield's (1960) study of the trophic hormone content of pituitary glands at necropsy did not reveal any difference between the pituitaries obtained from individuals who died from malignant disease and those who died from other causes. It is apparent that further investigation of the relation between pituitary gonadotrophin content, urinary excretion, and, if possible, circulating hormone is required before any final conclusion can be reached concerning the basic significance of the present results.

Although low levels of urinary gonadotrophins were, in general, associated with a poor prognosis in this series, their ultimate value as an empirical guide to prognosis after ablative endocrine procedures in women with carcinoma of the breast can be assessed only by prospective studies. Such a study is at present in progress in this department.

Summary

The results of 166 assays of urinary gonadotrophins in women with carcinoma of the breast are described. There was a significantly lower excretion of gonadotrophins in women who were unresponsive to hormonal therapy and in "poor" clinical condition. The significance of these findings is briefly discussed.

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Clinical Trial of Oxymorphone in Labour

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It is said (Roberts, 1959) that the ideal obstetric analgesic should have the following properties: (1) relieve pain; (2) not cause foetal asphyxia in effective doses; (3) not alter the course of labour; (4) have a reasonably quick disposal to obviate accumulation.

In the search for the ideal drug a clinical trial has been carried out on oxymorphone (Numorphan) (*B.M.J.*, 1962).

It is claimed that when used in the relief of post-operative pain (Coblentz and Bierman, 1956) and during general anaesthesia (Swerdlow and Brown, 1961) oxymorphone is approximately sixty times as potent as pethidine. Simeckova *et al.* (1960), in a preliminary report on its use with barbiturates in 100 parturient cases, claimed a high order of potency and a low incidence of side-effects.

Other clinical trials, using supplementary analgesia, have shown oxymorphone to be superior to pethidine in producing greater analgesia (Sentnor *et al.*, 1962) and in shortening the first stage of labour (Snow and Sattenspiel, 1962). However, Sherline and Roddick (1962), also using supplementary analgesia, could demonstrate no significant difference between oxymorphone and pethidine.

Chemistry.—Oxymorphone is a synthetic derivative of morphine chemically identified as 14-hydroxydihydromorphinone hydrochloride. Its synthesis from 14-hydroxydihydrocodeinone was first reported by Weiss (1955). It is

mainly detoxicated in the liver, and is excreted as conjugated glucuronate salts, mainly in the urine (Lewenstein, personal communication, 1964).

Method.

A pilot trial of 25 unselected cases in labour was carried out to confirm previous reports that it was an effective and safe analgesic. The drug met both these requirements.

A double blind trial was then carried out, using ampoules containing 1.5 mg. oxymorphone in 2 ml. saline and 100 mg.

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pethidine in 2 ml. saline. No other sedative or analgesic drugs were given. The ampoules were presented in four groups—two containing identical doses of oxymorphone and two containing identical doses of pethidine. Each group was given a code letter—J, K, L, or M—the key being known only to the chief pharmacist. When analgesia was first required each patient was allocated a code letter and given only the corresponding drug throughout labour. The initial dose was 1 or 2 ampoules, depending on the stage of labour; subsequent doses, if necessary, of 1 or 2 ampoules were given according to progress.

Immediately before administration the foetal heart rate and maternal respiratory rate, blood-pressure, and pulse rate were recorded. Subjective observations were made of the analgesic state and sedation of the mother. Further observations were made half an hour, one and a half hours, and three and a half hours after injection. The same trained observer was used in each case. Side-effects, such as vomiting, were recorded. The condition of the infant was assessed by means of the Apgar (1953) score at the time of delivery; this method of scoring takes into account respiration, heart rate, muscle tone, and response to stimulation. The time interval between the last injection and delivery was calculated.

All patients were entered for the trial, but cases requiring general anaesthesia during delivery were excluded. Also excluded were those not requiring a two-ampoule dose at any stage. A total of 148 patients completed the trial: 70 received oxymorphone, of whom 57% were primigravidae, and 78 received pethidine, 53% of these being primigravidae. For statistical purposes the unit of comparison is a two-ampoule dose.

Results

To judge the analgesic effect of the two drugs the subjective symptoms were noted under three columns—severe pain, pain, and discomfort without pain. A shift to the right, indicating relief of pain, was denoted as + (plus) for one column shift, and ++ (two pluses), for two. For example, an injection which reduces severe pain to pain, or pain to discomfort without pain is scored as + (plus); one which reduces severe pain to discomfort without pain, as ++ (two pluses); and similarly – (minus) and – – (two minuses) for changes in the reverse direction. The results have been scored by

allowing + 1 for + (plus), – 1 for – (minus), etc. For each time, the number of doses scoring each score for each drug has been tabulated. These scores have been analysed, using an analysis of variance. This compares the variance between the means for the drugs with the random or residual variation, and tests for significance. Half an hour after injection (Table I) of 103 doses of oxymorphone 74% had given relief, and of 102 doses of pethidine 63% had given relief. At no time after injection is there any statistically significant difference between the two drugs.

Sedation was assessed in a similar fashion, the columns indicating alert, drowsy, and asleep. Half an hour after injection (Table II), 81% of oxymorphone and 76% of pethidine produced sedation. Three hours later 44% of oxymorphone and 50% of pethidine still produced sedation. Again there is no statistically significant difference between these figures.

There were no stillbirths in this series. A total of 148 infants were born, of whom 146 were in good condition (Apgar score of 5 or more); 23 were delivered within two hours of the last injection, all of whom were in good condition. Of the two cases in which the infants required resuscitation, one was an uncomplicated breech delivery and the other a normal delivery. No statistically significant difference is shown between the two drugs (Table III).

TABLE III

Injection Delivery Interval (Hours)	Mean Apgar Score	
	Oxymorphone	Pethidine
2	8.0	8.3
2-3	9.2	8.6
3-4	8.6	8.4
4-5	8.9	9.3
5-6	8.6	10.0
6-7	9.5	6.7
7-8	10.0	8.3
8	9.8	8.1
Mean	9.1	8.5
Variance ratio	1.6 Not significant	

No obvious side-effects were noticed with either drug at this dosage. Ten patients vomited, 7 of these receiving pethidine. Neither oxymorphone nor pethidine appeared to have an adverse effect on the frequency of contractions or the duration of labour. There was no noticeable alteration in the

TABLE I

Change in Patient	Score	Number of Doses					
		½ hr. after Injection		1½ hr. after Injection		3½ hr. after Injection	
		Oxymorphone	Pethidine	Oxymorphone	Pethidine	Oxymorphone	Pethidine
Severe pain to discomfort without pain	+2	21 (20%)	17 (17%)	18 (20%)	15 (18%)	8 (14%)	3 (7%)
Severe pain to pain or pain to discomfort without pain ..	+1	55 (53%)	47 (46%)	40 (46%)	31 (38%)	25 (45%)	20 (46%)
No change	0	26 (25%)	35 (34%)	26 (30%)	31 (38%)	18 (32%)	14 (33%)
Discomfort without pain to pain or pain to severe pain ..	-1	1 (1%)	3 (3%)	2 (2%)	3 (4%)	5 (9%)	4 (5%)
Discomfort without pain to severe pain	-2	0	0	0	1 (1%)	0	2 (2%)
Number		103 (100%)	102 (100%)	86 (100%)	81 (100%)	56 (100%)	43 (100%)
Mean score		0.93	0.7	0.86	0.69	0.64	0.42
Variance ratio		2.67 Not significant		1.80 Not significant		1.50 Not significant	

TABLE II

Change in Patient	Score	Number of Doses					
		½ hr. after Injection		1½ hr. after Injection		3½ hr. after Injection	
		Oxymorphone	Pethidine	Oxymorphone	Pethidine	Oxymorphone	Pethidine
Alert to asleep	+2	10 (10%)	9 (9%)	15 (17%)	12 (15%)	1 (2%)	3 (7%)
Alert to drowsy or drowsy to asleep	+1	73 (71%)	67 (66%)	46 (54%)	52 (65%)	26 (47%)	18 (43%)
No change	0	20 (19%)	24 (24%)	25 (29%)	15 (19%)	29 (51%)	19 (45%)
Drowsy to alert or asleep to drowsy	-1	0	1 (1%)	0	1 (1%)	0	2 (5%)
Asleep to alert	-2	0	0	0	0	0	0
Number		103 (100%)	101 (100%)	86 (100%)	80 (100%)	56 (100%)	42 (100%)
Mean score		0.90	0.83	0.88	0.94	0.50	0.52
Variance ratio		0.84 Not significant		0.26 Not significant		0.03 Not significant	

maternal pulse rate, blood-pressure, or respiratory rate with either drug. The foetal heart was slowed with both drugs at half an hour, but that from oxymorphone was significantly greater than that from pethidine. However, this significance was only at the 5% level, and was not observed at later times.

To conclude, we have been unable to demonstrate that oxymorphone is superior to pethidine when the two are used alone as analgesics in labour. Past experience with drug mixtures—for example, pethidine and phenothiazine—has led to the strong clinical impression that they are more effective as analgesics and sedatives in labour than oxymorphone or pethidine alone. Certainly neither oxymorphone nor pethidine represents the ideal obstetric analgesic.

Summary

The analgesic and sedative effects of oxymorphone and pethidine have been compared in a double blind trial on 148 patients in labour. They are shown to be equally safe and effective. It is considered that neither oxymorphone alone

nor pethidine alone provides adequate relief of pain in labour.

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Medical Memoranda

Sodium Fluoride and Optic Neuritis

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Sodium fluoride has recently been reported to relieve Paget's disease of bone and idiopathic osteoporosis (Rich, 1960; Purves, 1962; Bernstein *et al.*, 1963). The report below is of a patient who developed bilateral optic neuritis six weeks after beginning sodium fluoride therapy for spinal osteoporosis.

CASE REPORT

The patient, a man born in 1906, developed severe thoracic backache in 1961, four months after a partial gastrectomy for a chronic duodenal ulcer. He was referred to King's College Hospital in September 1962. He was then thin, kyphotic, and tender over the thoracic spinal processes. He had early finger-clubbing and wheezed on exertion. His leg pulses were reduced, and shortly afterwards a femoro-popliteal by-pass graft was successfully done for a femoral-artery occlusion. Spinal radiographs showed partial collapse of several thoracic vertebrae, with apparent rarefaction of the bones and "fish-tailing" of the vertebral bodies. His serum calcium was 9.7 mg./100 ml.; serum phosphorus 3.4 mg./100 ml.; alkaline phosphatase 5 King-Armstrong units/100 ml.; acid phosphatase 3 units/100 ml.; and haemoglobin 93%. A fat balance was normal; a calcium balance revealed a urine calcium of 200 mg. daily on an 800-1,000-mg. calcium diet. His serum vitamin B₁₂ was 400 µg./100 ml. A chest radiograph showed old pneumoconiosis and fibrotic tuberculosis contracted in the coal-mines in his youth. As no evidence of osteomalacia, malabsorption, hyperparathyroidism, or bone tumour was found idiopathic osteoporosis was regarded as the cause of his bone disorder.

He was given Dianabol (methandienone) 10 mg. b.d. and calcium supplements for three months, but failed to improve. In February 1962 a total parathyroidectomy was done in the hope of reducing his bone breakdown. He went home a month later, taking Stanozolol 5 mg. b.d., calcium gluconate 5 g. t.d.s., calciferol 10,000 units b.d., and dihydrocodeine phosphate tablets.

As there was still no clinical or radiological improvement by the following August he was given sodium fluoride 20 mg. t.d.s.

orally along with his other drugs for six weeks. He then noticed pain and poor vision in his right eye, and five days later mistiness of vision in his left eye. He was readmitted to hospital, when he denied taking any other drugs, and his general state was found to be unchanged. His bone pain had not altered and there was no evidence of improvement of his skeletal radiographs. He was not cyanosed, there were no signs of latent tetany, both internal carotid arteries were palpable, and his blood-pressure was 130/85. There were no abnormal neurological signs except that ophthalmoscopy showed moderate oedema of the right optic disk, slight blurring of the left optic disk margin, and bilateral macular oedema. No haemorrhages or exudates were seen and the vessels appeared normal. The sight of his right eye was reduced to the perception of hand movements in the upper temporal periphery of the visual field. The corrected visual acuity of the left eye was 6/6 with some enlargement of the blind spot and constriction of the peripheral field. The right direct pupillary reaction to light was slight, though the consensual reaction was brisk. Ophthalmodynamometry showed normal and equal retinal-artery pressures. At this time his serum calcium was 9.4 mg/100 ml.; plasma phosphorus 3.2 mg./100 ml.; alkaline phosphatase 8 K.A. units/100 ml.; blood urea 28 mg./100 ml.; serum sodium 140 mEq/l.; potassium 4.5 mEq/l.; chloride 108 mEq/l.; and bicarbonate 28 mEq/l. His haemoglobin was 73%; E.S.R. 4 mm. in 1 hour (Westergren); a blood film showed anisocytosis and occasional burr cells. Both total and differential leucocyte counts were normal, as also were an E.C.G. and an E.E.G. Unfortunately we could not obtain urine- or serum-fluoride estimations at that time.

Treatment with sodium fluoride was stopped immediately and he was given prednisone 30 mg. daily. The oedema of the right disk began to subside two weeks later and a few small haemorrhages appeared but were soon absorbed. Two months later the right disk was pale and atrophic, and sight in that eye remained limited to the perception of hand movements in the upper temporal part of the visual field. The corrected visual acuity of the left eye remained normal. Final ophthalmic opinion (Mr. Pitts Crick) was that "the ocular condition appeared to be a bilateral toxic neuropathy, more marked in the right eye, where the changes proceeded to optic atrophy."

DISCUSSION

The toxicity of fluoride depends, among other factors, upon the dose ingested and the duration of intake. Large doses (4-