up to 16 hours. Proof when relying on subjective phenomena is always difficult. No such difficulty was found with placebo suppositories; indeed, the relapse was usually obvious next morning.

There was no practical difficulty in insertion of the suppositories except in patients with severe deformity of the hands, when a nurse or relative could do this instead. Patients pre-

FIG. 4.—Effect of indomethacin upon joint tenderness as shown by the cuff dolorimeter. B shows the decrease in tenderness of a proximal interphalangeal joint after 100 mg. by mouth, the corresponding serum level being shown in D. A shows the decrease in tenderness of the same joint after 100 mg. by rectum, the serum level being shown in C.

ferred to use the suppositories at night, as they were easily retained and were unaffected by defaecation, which is usually a morning habit. Local effects from the suppositories were noted in three cases. Sigmoidoscopy was performed in 10 patients, and the rectal mucosa was normal. Occult blood tests on the stools, performed routinely, showed no evidence of bleeding.

No dyspeptic symptoms occurred when suppositories were used, and systemic side-effects such as headaches or dizziness were negligible.

Thirty (75%) of the 40 patients given suppositories obtained a good result, and the clinical effects were similar whether the drug was given by mouth or by rectum. Certain patients who failed to respond to a daily dosage of 100 to 150 mg. were given larger doses, up to 300 mg. daily, by supplementing the oral doses with suppositories. This procedure might be effective, though it was more likely to produce side-effects.

Isolated serum levels were found to be of no practical value in controlling treatment. The peak serum level after rectal administration closely corresponded to one hour, though after oral administration it was too variable to be predictable. The maximum serum levels obtained in different patients did not equate with the degree of relief of pain or the severity of side-effects in these patients.

Discussion

This trial has shown that indomethacin is a valuable drug for the treatment of patients with various types of arthritis. Relapse when a dummy tablet or suppository is substituted is striking and sometimes suggests a "rebound effect." Its use may enable corticosteroid therapy to be reduced in some patients and occasionally to be discontinued altogether.

Capsules are suitable for routine use, although suppositories can be prescribed for the following reasons: (1) when oral administration is contraindicated because of dyspepsia or peptic ulceration, and (2) to increase the total daily dosage above limits now regarded as safe when given by mouth (such as 150 mg. daily).

Side-effects have been no more than an inconvenience, and, in particular, no gastric disturbance has occurred in our trial. It is not yet known why oral indomethacin, like other analgesic or anti-inflammatory drugs, may injure the stomach. If the disturbance is due solely to local damage to the mucosa it should be avoided by rectal administration. If, however, indomethacin causes an increase in the hydrochloric-acid secretion or a decrease in mucosal resistance from a systemic action, there may still be a risk of this after suppositories.

Summary

The estimation of serum levels of indomethacin has shown that it is absorbed satisfactorily from the rectum.

Suppositories containing this drug can be used when capsules are contraindicated because of peptic ulcer or to supplement the total daily dosage.

Indomethacin is a valuable drug for the treatment of patients with various types of arthritis.

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Adrenocortical Carcinoma Treated with *o,p'*-DDD

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The modern chemotherapy of adrenocortical carcinoma stems from the observation by Nelson and Woodard (1949) that the insecticide DDD¹ induced a selective necrosis of the zona

¹ TDE is now the British standard name for DDD.

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fasciculata and zona reticularis of the adrenal cortex in dogs. Initial efforts to use it in man were unsuccessful (Sheehan *et al.*, 1953; Törnblom, 1956; Zimmermann *et al.*, 1956). However, the subsequent discovery that a contaminant of crude DDD, the ortho prime isomer *o,p'*-DDD (2(2-chlorophenyl)-2-(4-chlorophenyl)-1,1-dichlorethane) (Fig. 1), was a much more effective drug, led to further investigation of its action in the treatment of adrenocortical cancers. Reports of its use in a

number of cases have appeared recently (Bergental *et al.*, 1960 ; Verdon *et al.*, 1962 ; Fisher *et al.*, 1963 ; Molnar *et al.*, 1963 ; Netto *et al.*, 1963).

o,p'-DDD appears to destroy adrenocortical tissue directly. It is given by mouth in a dose of 6 to 10 g. daily. Young subjects with hormonally active tumours respond best, but most relapse subsequently, and many are quite uninfluenced by the drug. In those who respond favourably the urinary excretion of adrenal steroids falls to low levels and replacement therapy with cortisone is often necessary. Toxic reactions are common and involve the alimentary tract, the skin, and the central nervous system.

FIG. 1.—Structure of *o,p'*-DDD and related substances.

We record here our experience with *o,p'*-DDD in the treatment of a child with metastases from an adrenocortical carcinoma which had caused Cushing's syndrome.

Case History

A girl aged 3 years and 4 months was admitted to hospital on 22 May 1963 with a history of increasing weight for seven months, growth of pubic hair for six weeks, and pain on micturition for two weeks. She was the second child of healthy unrelated parents, weighed 6 lb. 10 oz. (3 kg.) at birth, and had previously been normal.

She was obese and had a rounded face with a high colour. A large mass which moved freely with respiration was felt in the left hypochondrium. The blood-pressure was 150/60, and there was a pronounced growth of pubic hair.

Investigations.—Haemoglobin 10.2 g./100 ml. ; white-cell count 7,800/c.mm. (neutrophils 48%, lymphocytes 46%, monocytes 6%) ; plasma electrolytes normal ; fasting blood glucose 109 mg./100 ml. ; serum calcium 9.9 mg./100 ml. ; serum phosphorus 5.3 mg./100 ml. ; urinary 17-oxosteroid excretion 129 mg./24 hours ; urinary 17-hydroxysteroid excretion 10.1 mg./24 hours. X-ray films of the skull, chest, and spine showed nothing abnormal. An intravenous pyelogram showed a large non-opaque mass depressing the left kidney. X-ray examination of the carpal bones revealed six centres of ossification (bone age 6–7 years).

Treatment.—A diagnosis of an adrenocortical carcinoma with Cushing's syndrome was made, and surgical removal of the tumour under cortisone replacement was advised and carried out on 28 May. At operation a large tumour weighing 700 g. was found replacing the left adrenal gland. The mass was mobilized and its single artery, which arose from the left renal artery, was divided and ligated. The adrenal vein was enlarged and packed solid with tumour tissue which extended for about an inch (2.5 cm.) into the inferior vena cava. Before the adrenal vein was ligated it was incised and the tail of the tumour tissue was milked back from the vena cava and removed through the opening in the adrenal vein. The growth was resected and the wound closed in layers without drainage. Post-operative recovery was delayed slightly by a mild chest infection. Cortisone was withdrawn gradually after the operation, and stopped on the twelfth day. The urinary 17-oxosteroids and 17-hydroxysteroids fell to 2.9 and 2.2 mg./24 hours respectively 12 days after removal of the tumour.

Pathology of Tumour (Professor W. T. E. McCaughey).—The adrenal tumour was encapsulated and oval in outline. On section there was considerable necrosis and vascular thrombosis, and only a small portion of the tumour appeared viable. Histologically the growth consisted mainly of sheets of cells with poorly demarcated

granular acidophilic cytoplasm and prominent round or oval nuclei with moderate chromatin content. In some areas the cells were more irregular in appearance, and scattered giant cells with multiple nuclei or large and often hyperchromatic nuclei were seen. The adrenal vein was occluded by a mass of partly necrotic tumour tissue.

After operation she improved and had an excellent remission of Cushing's syndrome. At the end of September, however, x-ray examination of the chest showed probable early metastases and she was admitted to the metabolic unit of the Royal Victoria Hospital on 10 October. She looked and felt well and weighed 35 lb. (15.9 kg.). There were no features to suggest a recurrence of Cushing's syndrome. The liver was enlarged slightly, but its edge was soft and not nodular. The blood-pressure was 140/85, the haemoglobin 12 g./100 ml., and the urinary 17-oxosteroids and 17-hydroxysteroids were 21.4 and 7.8 mg./24 hours respectively. X-ray examination of the chest now showed multiple small discrete deposits in both lung fields, and it was clear that the disease was advancing rapidly.

Treatment with *o,p'*-DDD was considered desirable, but the drug could not be obtained until the end of December and treatment was started on 6 January 1964. At this time the liver had enlarged considerably and was nodular and hard. The metastases in the lungs were larger than in the previous x-ray films and continued to enlarge for a month after the start of treatment (Fig. 2). The

FIG. 2.—X-ray film of chest taken on 7 February 1964, showing the pulmonary metastases at their worst.

FIG. 3.—Dosage of *o,p'*-DDD and cortisone correlated with body weight, findings on palpation of liver, and urinary excretion of steroids.

17-oxosteroid excretion had risen to 85 mg./24 hours, the plasma cortisol level was 43 mg./100 ml., and the haemoglobin was 11.2 g./100 ml. *o,p'*-DDD was first given in a dose of 3 g. daily and gradually increased to 8 g. daily four weeks later. Cortisone acetate was also started at this time. The subsequent progress and response to *o,p'*-DDD is recorded in Fig. 3. The drug was fairly well tolerated and no definite toxic effects on the haemopoietic system or change in liver-function tests were noted. There were occasional bouts of nausea and vomiting, but it was not clear whether they were due to the *o,p'*-DDD or to the disease.

The patient was discharged from hospital on 8 February and attended the out-patient clinic regularly. By 23 March there was marked regression of the pulmonary metastases, the liver was becoming smaller and softer, and the 17-oxosteroid excretion had reached almost normal levels for a child of this age. Her last visit to the hospital was a month later, when progress was satisfactory. The metastases in the lungs has shrunk still further (Fig. 4). Ten days later she died suddenly, having apparently developed a febrile illness, possibly measles, two days before death.

FIG. 4.—X-ray film of chest taken on 20 April 1964, showing considerable regression of pulmonary metastases.

Post-mortem Examination (Professor W. T. E. McCaughey).—The liver was enlarged and weighed 850 g. On section the substance of the left lobe was permeated by bands of pale yellow tumour tissue which produced a nutmeg-like pattern. No discrete tumour nodules were present, but carcinomatous tissue was observed in several large venous channels in the substance of the left lobe. The right side of the liver, in spite of its enlargement, showed no evidence of tumour infiltration. Microscopically, sections from the left lobe revealed extensive permeation of the portal venous system and the tumour was largely or entirely confined to the portal areas. Almost all the growth appeared viable. The lungs contained nodules of tumour tissue varying in diameter from 1 cm. to less than 5 mm. Histologically these were situated in the vicinity of pulmonary arterioles. Some nodules were necrotic but others were viable and consisted of irregularly disposed large cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei. The right adrenal weighed 2.3 g. and was smaller than normal. The cortex

was thin and composed of large, pale cells that resembled those seen in persons receiving prolonged cortisone therapy. The intra-abdominal lymph nodes were searched for tumour tissue but no evidence of metastases was found.

Discussion

It is clear, from the clinical, radiological, and biochemical findings, that *o,p'*-DDD caused considerable regression of metastases in the liver and lungs without obvious toxic effects. Necropsy, however, revealed large deposits of tumour remaining in these organs. There were no histological features which could be attributed unequivocally to the action of the drug on the tumour. Much of it was necrotic, but necrosis had been a prominent feature of the primary growth. Many cells in the metastases were of a "plumper" type than those in the primary, but such cells are common in other adrenocortical carcinomas.

The effective dose of *o,p'*-DDD was about 8 g. a day, which is very high for a child of 3 years. No regression was apparent until this level was reached; in fact the pulmonary metastases continued to grow while smaller doses were being given. Earlier administration of the drug might have been more effective.

Summary

A girl aged 3 years had a large adrenocortical carcinoma causing Cushing's syndrome. Removal of the tumour caused a good clinical and biochemical remission but was followed by massive metastases in the liver and lungs. These regressed considerably under therapy with *o,p'*-DDD but the patient died four months after treatment had been started.

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