the toad *Bufo marinus* it was given in doses of 1·2-2·4 g per day to three patients with diabetes insipidus. In each the volume of urine and clearance of free water fell.[2] Thiazide diuretics have also been given, with varying success, to patients with diabetes insipidus.[3] The mechanism of this effect has never been wholly understood, but it is probably related to their natriuretic action. Thiazides are probably of greater use for patients with nephrogenic diabetes insipidus who are resistant to vasopressin.

The most effective drug apart from vasopressin for the treatment of diabetes insipidus is the sulphonylurea, chlorpropamide. Like many other important advances in clinical therapeutics this was made by chance—or rather by the error of a patient, a 37-year-old man in Rio de Janiero who, believing he was suffering from diabetes mellitus, prescribed chlorpropamide for himself.[4] So successful were the results that his physicians gave chlorpropamide to four other patients, two with nephrogenic diabetes insipidus and two with the idiopathic vasopressin-dependent variety of the disease. Both patients with the latter type responded but neither with the former type.

In the successful cases there was a considerable fall in the urine volume and a decrease in both the urine osmolarity and free water clearance, but no change in the osmolar clearance or glomerular filtration rate. Thus the results were very like those obtained with vasopressin. In their original report F. Arduino and his colleagues[4] postulated that these changes might be due, firstly, to chlorpropamide directly stimulating the release of antidiuretic hormone from the pituitary, or secondly to restoring the response of insensitive osmoreceptors to normal stimuli, or thirdly to a direct action of the drug on the kidney. Some support for the first of these explanations comes from the work of B. Ettinger and P. H. Forsham,[5] though they made no measurements of circulating levels of antidiuretic hormone. Against this theory is the observation[6] that patients with familial congenital diabetes insipidus, who are thought to have no antidiuretic hormone in the posterior pituitary, respond to chlorpropamide. Likewise the second explanation, that of restoration of osmoreceptor sensitivity, seems untenable, since delayed excretion of water after water loading is seen in patients with diabetes insipidus on chlorpropamide. The idea that a drug structurally dissimilar to the natural hormone may act in the same way as the hormone itself is puzzling. J. H. Mahoney and A. D. Goodman[7] have tried to explain this paradox by suggesting that 3′, 5′-adenosine monophosphate (cyclic AMP) mediates the action of vasopressin and of chlorpropamide on the pancreas in diabetes mellitus and on the kidney in diabetes insipidus. It seems unlikely that the action of chlorpropamide in diabetes insipidus is related to its hypoglycaemic action, because other agents that lower the level of the blood sugar, such as insulin, have no such effect.

Chlorpropamide has an important therapeutic role in the treatment of vasopressin-dependent diabetes insipidus, but not in the treatment of the nephrogenic (vasopressin-resistant) form of the disease. The side effects of vasopressin—intestinal discomfort, headache, rhinitis, and, more seriously, angina in patients with ischaemic heart disease—can be so unpleasant that some patients prefer to put up with the symptoms of the disease rather than take vasopressin. It is for these patients that chlorpropamide is of greatest use.

The effectiveness of this drug has been challenged, however. A. G. Hocken and D. Longson[8] found that two out of three patients with idiopathic diabetes insipidus showed no response to 250 mg or 500 mg chlorpropamide given by mouth. In two patients with both anterior and posterior pituitary disease chlorpropamide therapy has been found ineffective.[9] Furthermore, several reports[10 11] have stressed that the hypoglycaemia produced by chlorpropamide may limit its usefulness. One patient, an eight-year-old boy whose diabetes insipidus had been well controlled with parenteral vasopressin, had hypoglycaemic convulsions when chlorpropamide was substituted.

Several interesting pharmacological points are raised by the use of chlorpropamide in diabetes insipidus. Its effect is dose-dependent, and several days elapse before the response is optimum. This is presumably related to the achievement of an adequate plasma concentration of the drug. The effect can last for as long as 10-15 days after withdrawal of the drug; though chlorpropamide lasts longer in the plasma (half-life some 30-40 hours) than other sulphonylureas, this duration of effect is remarkable. Finally, why this drug and no other sulphonylurea should be effective is peculiar. The biguanide, metformin, another oral antidiabetic drug, has also been found effective in patients with diabetes insipidus,[11] but it has not been investigated so thoroughly as chlorpropamide.

Apart from its therapeutic interest, the manner of chlorpropamide's action may, when it is elucidated, shed further light on the molecular basis of diabetes insipidus.

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Marginal Ulceration of the Cornea

A painful red eye is a common diagnostic problem. Apart from minor foreign bodies, the usual causes are conjunctivitis, anterior uveitis (iritis), acute closed-angle glaucoma, and keratitis. It is this last cause which receives the least attention, particularly as specialized equipment (such as a slit lamp) is often required to establish the diagnosis. Nevertheless, some forms of keratitis are easy to recognize with nothing more than a torch, and one of these is simple marginal ulceration of the cornea. This by no means uncommon condition presents as a painful red eye with a round ulcer overlying an obvious grey to white infiltrate. The ulcer is about 1 mm in diameter with a clear zone of cornea separating it from the limbus, and the conjunctiva is injected locally. The lesion may clear spontaneously in about a week but it is often surprisingly painful and it frequently recurs.

A. H. Chignell and his colleagues have recently reported on 84 patients with marginal ulceration of the cornea seen over a period of one year.[1] They point out how closely the symptoms resemble those of a corneal foreign body. Pathogenic staphylococci have long been suspected of being a cause of this condition, and in this study almost a third of the patients were

found to have these organisms in the conjunctival sac. Nevertheless, the examination of scrapings taken directly from the ulcer suggested that the lesion is a non-infective inflammation.

The authors also found that a quarter of their patients had recently had or were suffering from an upper respiratory tract infection.

Three methods of treatment were tried. Carbolization of the ulcer meant that the eye had to be bandaged for at least two days, and since this treatment in no way shortened the course of ulceration Chignell and his colleagues concluded that it should be abandoned. The other two methods were compared in a controlled study. Prednisolone eye drops were found to be highly effective whereas neomycin eye drops had no appreciable effect on the course of the ulcer. Thus most patients were cured using prednisolone drops every two hours for three to four days, without the inconvenience of either using mydriatics or having the eye bandaged. The response to steroids supports the belief that the ulcer is not infective in nature, though in some cases it may be due to hypersensitivity or a toxic response to pathogenic staphylococci.

The introduction of eye drops containing broad-spectrum antibiotics and steroids has proved of great value in the treatment of local eye disease. However, they are often used with little or no regard to the underlying condition, and unless a careful inspection and history are taken serious mistakes may occur. It is still quite common to find acute closed-angle glaucoma treated as conjunctivitis, when a simple test of the patient's vision and an inspection of the cornea, quite apart from feeling the tension digitally, would indicate the correct diagnosis. The use of combined antibiotic and steroid drops in the treatment of herpes simplex keratitis may lead to a disastrous extension of the ulcer. In these cases the association with oral herpes and the use of fluorescein should indicate the true nature of the lesion. If there is any suspicion of a herpetic ulcer local steroids must not be administered.

This recent paper emphasizes once again the value of simple inspection of the eye, which in the case of simple marginal ulceration of the cornea can lead to a correct diagnosis and easy and successful treatment.

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Nephroblastoma and Neuroblastoma in Children

It is good news that the Medical Research Council is conducting clinical trials of the treatment of nephroblastoma (Wilms's tumour) and neuroblastoma.[1] [2] These tumours are rare but tragic in their consequences. The incidence of nephroblastoma in children is about 1 in 200,000 children under 14, and few if any surgeons or radiotherapists have enough personal experience to be justified in making confident and dogmatic statements about their treatment. It is notoriously difficult to compare the results obtained by one unit with those of another, because of variables such as the age of the child, the site of the tumour, and the stage of disease when first seen. Moreover, there is an almost infinite number of possible variations in the nature and timing of treatment by surgery, chemotherapy, radiotherapy, or immunotherapy. To obtain the answer to only one question about which of two treatments is the better some years are required. Hence it is important to ask the right questions before embarking on research into treatment.

Experts from centres in the United Kingdom have held a series of meetings to hammer out one trial of the treatment of nephroblastoma and one of the treatment of neuroblastoma. The treatment of both is unsatisfactory, that of nephroblastoma being the better, some 30 to 40% of patients surviving three to five years. An Oxford survey of 335 cases in England and Wales between 1962 and 1966[3] showed a three-year survival rate of 35% after nephrectomy; the other two-thirds suffered recurrences, almost all within two years of the onset of the disease. Metastases are mainly pulmonary, but workers at Liverpool[4] were able to report that 7 out of their 16 cases with lung metastases were alive for periods of 18 months to 21 years after treatment.

An American survey[5] of 168 cases of nephroblastoma found that there had been a significant improvement in the prognosis since 1956, due in part, it was thought, to actinomycin D and vincristine, but in a corresponding survey of 226 cases of neuroblastoma there had been no significant improvement in the outlook despite advances in surgical, radiotherapeutic, and other treatment. The survival rate for neuroblastoma is about 60% for two years in children under 12 months, but only 21% for those aged 1 to 2 years, 10% for those aged 2 to 7, and 8% for those aged 7 to 19. In a study of 48 children with generalized neuroblastoma[6] 36% survived for a year, but all but two had died within 26 months. Such results are disappointing, and to obtain them drugs with troublesome side effects, such as actinomycin D or vincristine, have to be used. Vincristine is probably less toxic than actinomycin D, but the latter may be more effective in preventing metastases. One of the objects of the M.R.C. trial is to compare the effect of vincristine with actinomycin D. In all cases the tumour will be operated on as soon as possible, and actinomycin D will be given on the day of the operation. For two years an agreed course of radiotherapy will be followed by random selection for either actinomycin D or vincristine.

In the case of neuroblastoma the clinical trial has been designed to investigate whether the regression that sometimes occurs is the result of an immune reaction against the tumour, and if so whether the immunity can be increased by immunotherapy. There is evidence that immunity against the tumour is likely to be successful only when the number of cells is relatively low, and attempts at immunotherapy will therefore follow cytotoxic chemotherapy by vincristine and cyclophosphamide. Surgical removal, when feasible, and radiotherapy will be followed by alternating vincristine and cyclophosphamide; in random order the patients will then be given immunotherapy or chemotherapy. Children under 12 months of age and those with the primary tumour confined to the cervical region will be excluded. The primary tumour will be investigated for its antigen content, and the child's and mother's lymphocytes will be tested for specific immune activity. Specimens will be sent to the Institute of Cancer Research in Surrey.

It says much for the spirit of co-operation between scientists that these two trials are possible. They entail the co-operation of the Southern Tumour Group Committee, under the chairmanship of Dr. White Franklin, the Northern and Glasgow Group, and the Tumour Committee of the Hospital for Sick Children, Great Ormond Street, London, under the chairmanship of Professor Andrew Wilkinson. All these groups have themselves been conducting trials for some years. In addition the trial would have been impossible without the help of radiotherapists, who arrived at an agreed regimen of treatment, of pathologists for the examination of specimens,