me. It may work, but if the assay picks up both relevant and irrelevant isozymes it maybe worse than useless. It may be misleading.

Organisms have made use of organic compounds having elemental reactive sites since their inceptions. We have used more simple organometallic compounds in medicine almost as long as chemists have synthesized them. Such complexes of mercury, antimony, and gold have stood us in good stead for many decades for the treatment of syphilis, as diuretics for the relief of edema, the treatment of schistosomiasis and the management of arthritis.

You may know that safety of such compounds is almost as important as efficacy, but you probably have no idea how to go about bringing an interesting agent from theory to therapy. The purpose of this lecture is to explain how you might go about making a new drug out of an interesting agent today; the excitement, the pitfalls, the time, the cost and «what's it to you».

RT1.4 — MO

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LITHIUM IN MEDICINE

Lithium has been used in medicine since the middle of the nineteenth century. However, it has been used extensively only in psychiatry and only since 1949 when CADE [1] first discovered the "anti manic" action. Latterly this was exploited by SCHOU [2,3] who recognised the significant prophylactic, or preventative, action against recurrent mood swings in periodic affective disorders, the manic depressive psychoses. Currently some 25,000 patients in the United Kingdom (1 in 2000 of the population) receive lithium therapy.

The biochemical basis of the action of lithium, and indeed the aetiology of the disease itself, has been extensively studied but so far a solution eludes us [4]. A number of side effects of lithium has been frequently described and these, themselves, have become the bases for a number of medical uses of lithium. In particular its use in granulocytopaenia, a deficiency of specific white blood cells, granulocytes, has been documented in a major review volume by ROSSOF & ROBINSON [5] Lithium has also been used in attempts to elucidate mechanisms and provide a diagnostic test in essential hypertension where it may interact with sodium transport mechanisms [6].

In psychiatric practice lithium is always given orally, a dose of up to 1 g lithium carbonate per day being usual and with the objective of maintaining the blood plasma concentration of lithium in the range 0.6-1.2 mmol/l. Excessive plasma lithium is an indication of impending toxicity which may result from overdosage (accidental or with suicidal intent) reduced fluid or salt intake, excessive sweating or dietary restriction. Toxicity is best treated by haemodialysis which must be maintained until the body burden of lithium is significantly reduced. Practical aspects of therapy have been comprehensively discussed by JOHNSON [7].

In an attempt to prevent the wide daily excursions in plasma lithium shown following the administration of conventional lithium carbonate preparations on a normal regime, slow release formulations have been used in which the lithium carbonate is either embedded in a waxy or cellulose matrix or very highly compressed. The efficacy of these has been questioned and we have carried out a series of studies to identify the mode of transfer of lithium across the gastrointestinal tract [8,9].

Recent fears that lithium might cause permanent renal damage in long-term therapy have now been largely discounted though there still remains some doubt of the safety of combinations of lithium with other major psychotropic drugs over a prolonged period. Combination of lithium therapy with other long-term psychotropic therapy therefore is best avoided.

It has been suggested that lithium may act by interference with magnesium dependant processes due to the chemical similarity between the two ele-

ments resulting from the diagonal relationship in the periodic table [10]. Kinetic studies of magnesium dependant enzymes and investigation by NMR of interactions of lithium and magnesium with nucleotides [11], have shown only weak effects of lithium on magnesium regulated processes and the working hypothesis must therefore be reconsidered.

Lithium carbonate is a useful and inexpensive drug which has an important role to play in current therapeutics. Its mode of action is not well defined and much scope therefore remains for further study in this area of Inorganic Pharmacology.

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RT1.5 — MO

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CLINICAL APPLICATIONS OF PLATINUM METAL COMPLEXES

In the late 1960's ROSENBERG noted that the growth of bacteria exposed to an electric field became filamentous, suggesting the presence of an antiproliferative agent in the culture medium. This observation led to the identification of *cis*-dichloro-diammine platinum II (cisplatin) as a possible anticancer agent [1]. Subsequent clinical studies performed initially in the USA and England, but later throughout the world have established cisplatin as one of the most important new anticancer drugs to enter clinical practice in the last ten years [2]. Its use in combination in the treatment of testicular tumours has transformed the prognosis. Even for patients with disseminated disease cure rates in the region of 90% are now achieved in most major centres [3]. Cisplatin is also the prime agent in ovarian cancer [4] and is active in a variety of other tumours.

Cisplatin is capable of forming adducts to nucleophilic sites on biological molecules, the chorine atoms acting as leaving groups. In common with a number of other anticancer drugs, cisplatin will cross-link DNA via the guanine residues. The property of cisplatin which endows it with its special activity is not known. However, cisplatin is capable of forming intrastrand cross-links [5] and it is tempting to speculate that these differentiate its activity from that of other drugs. The analogue transplatin possesses most of the biological properties and toxicities of cisplatin but is both devoid of antitumour effect and incapable of forming intrastrand cross-links.