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from the limb uninvolved by Paget's disease, the increased vasculature of Paget's disease is thought not to be primarily a result of increased bone metabolism. Passage of a renal calculus as in this patient is thought to occur more often in patients with Paget's disease than in a control population. Transient hypercalciuria might explain this observation and stone formation is not directly linked to the Pagetic process itself.

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Effect of Phenytoin and Other Drugs in Reducing Serum DDT Levels

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SUMMARY

Patients on long-term anticonvulsant treatment with phenytoin (diphenylhydantoin) have been shown to have markedly reduced blood levels of DDT-derived materials. Establishment of reduced equilibrium levels appears to take some 12 months. Although phenytoin is especially effective, long-term treatment with a wide variety of other therapeutic substances has been shown also to reduce blood levels of DDT-derived material. Possible mechanisms determining the reduction are discussed.

INTRODUCTION

Davies and others (1969) reported reduced levels of DDT and DDE in fat and blood of patients receiving anticonvulsant drugs when compared with a similar outpatient hospital population. Phenytoin appeared to be specially effective in this regard but phenobarbitone was also moderately active. Schoor (1970) showed that blood levels of DDT and DDT-derived material were markedly lower in blood from a farmer on treatment with phenytoin and phenobarbitone than in blood from other farmers from the same heavy pesticide use area. Levels of other organochlorine pesticides were also lower.

Kwalick (1971) observed extremely low levels of DDT and DDE in serum from a pesticide formulator on phenytoin and phenobarbitone which contrasted strikingly with the high blood levels in other employees in the same plant.

Davies and others (1971) gave 300mg phenytoin daily to volunteers for up to nine months and

observed significant depletion of residues of DDT and DDE as well as other organochlorine pesticides in adipose tissue biopsy samples.

The mechanism of this organochlorine pesticide depletion is not definitely known. Phenytoin and phenobarbitone are inducers of hepatic microsomal enzymes and increased metabolism may explain the reduced levels. Schoor (1970) suggested competition of drugs and pesticides for the same binding sites on proteins, the resultant displacement of the pesticides rendering them more available for metabolism.

In the present study the blood levels of patients under treatment with phenytoin have been compared with those from subjects not receiving any drug therapy. The relationship between duration of phenytoin therapy and serum DDT-derived material has also been studied. To assess the specificity of phenytoin in reducing the pesticide levels, blood from a large number of patients on long-term treatment with other drugs was also examined.

METHODS

The majority of the control samples of serum were obtained from the Otago Regional Blood Transfusion Unit. These included samples obtained from donors in both urban and rural areas. Persons on systematic drug treatment for any important disorder are not accepted as donors although occasional medication, and in the case of women, oral contraceptives, would not have excluded. Additional control samples were contributed by unit staff members, associated workers and friends.

The phenytoin samples were from inpatients and outpatients at the Dunedin and Wakari Public Hospitals and detailed accounts were available of the nature and duration of their medication.

Samples from patients on long-term therapy with therapeutic substances other than anticonvulsants were also obtained from patients at the above hospitals, and also from inpatients at the Cherry Farm Psychiatric Hospital on long-term psychiatric treatment.

Pesticide Analysis.—Samples of serum (2ml) were heated in 40ml glass-stoppered centrifuge tubes with 2.5 percent KOH in ethanol (10ml) for one hour at 78°C. After cooling, redistilled hexane (10ml) was added and the tubes were shaken vigorously for 10 minutes on a mechanical shaker. The aqueous phase was aspirated and discarded. The extracts were washed by hand shaking gently with saturated Na_2SO_4 (10ml). An aliquot of the hexane layer was analysed by gas chromatography. All glassware was pre-rinsed with hexane and the Na_2SO_4 was extracted with hexane before use.

Saponification.—Saponification of samples before extraction was used because it was found to give consistently excellent recoveries of pp'–DDT and pp'–DDE added to serum. Saponification also serves as a "clean up" step, making possible accurate quantitation of the low levels found in phenytoin patients. An additional advantage is that the response of pp'–DDE in the gas chromatograph is four times that of pp'–DDT. The saponification technique gives recoveries of 97.8 percent for pp'–DDE and 98 percent for pp'–DDT added to serum. In the saponification step pp'–DDT is dehydrochlorinated to pp'–DDE so that the pp'–DDE level reported is the sum of pp'–DDT and pp'–DDE.

The pp'–DDE analyses were performed on a Varian Aerograph model 2100 gas chromatograph fitted with tritium electron capture detectors. The columns used were 1.8m by 2.4mm i.d. pyrex glass packed with a mixture of 2 percent OV–1 and 3 percent OV–210 on 100/120 mesh AWDMCS treated Chromosorb W. The operating conditions were: injector block 215°C, column 180°C, detector block 275°C and nitrogen carrier gas flow rate 25ml/min.

RESULTS

The levels of DDT and DDE, i.e., the virtual total of DDT-derived material, DDE being the major metabolic and principal storage form, are shown in Table I. Levels for each of the three groups, no-medication control, long-term treatment other than anticonvulsant, and phenytoin treated, are shown and these are also illustrated in Figure 1. With regard to the two treated groups, only patients on therapy for more than three months are included.

TABLE I

	No.	Mean (ng/ml)	Median (ditto)
Control	170	44.1	39.6
		$P < 0.001$*	
Other drugs	100	26.1	23.5
		$P < 0.001$*	
Phenytoin	28	10.3	6.6

* Significance of differences between means.

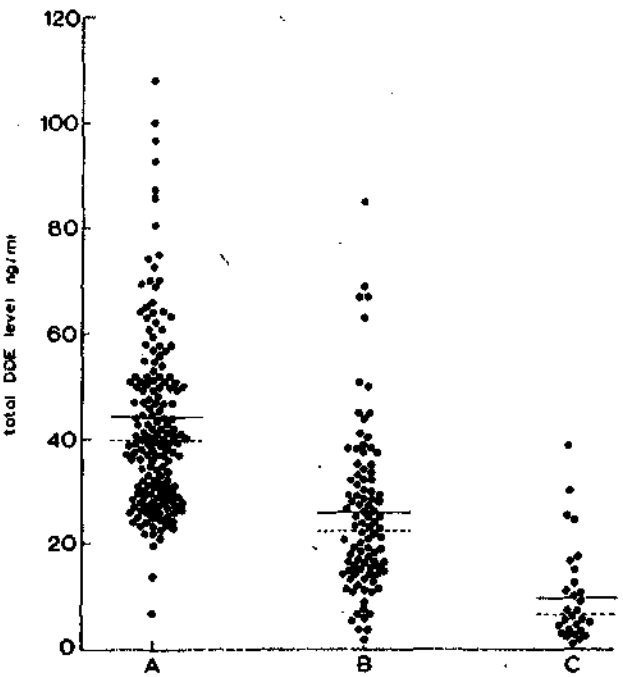

FIGURE 1.—Serum DDT/DDE levels (ng/ml) in untreated controls (Group A), patients on long-term treatment with drugs other than anticonvulsants (group B), patients on long-term treatment with phenytoin (group C).

Treatment with phenytoin for more than three months markedly reduced the mean (and median) values. Treatment with drugs other than anticonvulsants for more than three months was also associated with a lesser but still highly significant fall.

The relationship between duration of treatment with phenytoin and DDT-DDE level is shown in Figure 2. The regression of DDT-DDE levels on time is highly significant ($P < 0.001$).

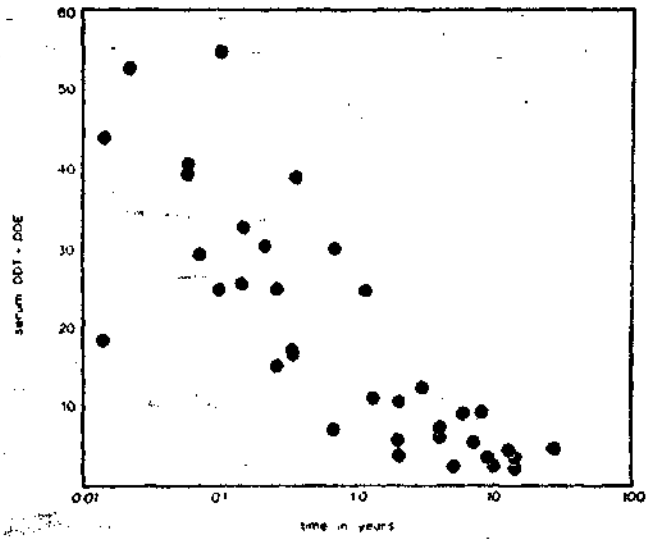

FIGURE 2.—Relationship between serum DDT/DDE ng/ml (ordinate) and duration of phenytoin treatment in years (abscissa).

DISCUSSION

The levels of DDT and its metabolites in blood and tissues of human subjects in the absence of unusually intense acute exposure or sudden loss of weight are reasonably constant for a given individual, being maintained by an equilibrium established between dietary intake and disposal from the body. By far the greater proportion of the "body burden" is in adipose tissue where DDT and its major storage metabolite DDE are largely sequestered by virtue of their extreme lipid solubility and correspondingly low solubility in water. Distribution between tissues is largely a function of their fat content (Morgan, Roan, 1970).

In the plasma, DDT and DDE appear to be exclusively carried in the first peak on Sephadex column fractionation, i.e., the peak containing the lipoprotein (Ferry and others, 1972).

Intake of DDT is the most obvious determinant of the levels in the blood and tissues (Durham, 1969), intense occupational exposure, as in pesticide formulations being accompanied by levels as much as 20 to 30 times higher than the average of the population (Poland and others, 1970). In the absence of specially intense exposure, the intake of these pesticides in the food is probably fairly uniform and although variations in domestic use of insecticide sprays may be responsible for some of the range of values seen in blood and tissue levels of normal subjects, individual variations in the rate of disposal probably play an important part.

The present experiments confirm the observations of Davies and others (1969), Schoor (1970) and Kwalick (1971), in respect of the marked reduction of DDT-derived material in the plasma produced by chronic dosage with phenytoin. The mechanism whereby this is brought about is generally presumed to be via enhanced hepatic biotransformational activity. Phenytoin is a well-known stimulant of liver microsomal enzyme activity in other contexts (Conney, 1967).

The time course of reduction to a new equilibrium level which would appear from our results for blood to be about a year and from those of Davies and others (1971) for adipose tissue to be approximately the same is in conformity with the time taken to reach a new high level equilibrium with increased intake (Hayes and others, 1956).

One somewhat puzzling aspect of the reduction of body burden by phenytoin is that the levels of DDT and DDE fall in parallel (Davies and others, 1971) in spite of the paucity of data to indicate an enzymal pathway for further degradation of DDE in man (Roan, Morgan, Paschal, 1971).

An alternative suggestion put forward by Schoor (1970), is that phenytoin acts by displacing DDT from binding to plasma proteins, thereby rendering it more susceptible to metabolic processes. However, although phenytoin is a specially effective displacing agent, displacing for instance thyroxine from its specific carrier globulin as well as displacing other anionic drugs from albumin, the nature of the association of DDT with its carrier fraction is probably quite different and a function of lipid solubility rather than binding to protein (Ferry and others, 1972).

Many substances other than phenytoin are known to enhance the activity of hepatic microsomal enzymes affecting the metabolism of drugs, phenobarbitone particularly, but also a large variety of agents including many other hypnotics, sedatives and anticonvulsants, psychotropic drugs, anti-inflammatory agents and insecticides including DDT itself (Conney, 1967). It would appear from our findings that long-term treatment with a variety of therapeutic substances may have a significant effect in reducing the equilibrium levels of DDT-derived material, thus conferring a somewhat unexpected bonus on the recipients. Although only very high levels of DDT have been shown to have overt effects on metabolic processes in humans, and these of a largely theoretical character (Poland and others, 1970) it is a reasonable presumption that the lower the body burden of these ubiquitous compounds the better.

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Iatrogenic Drug Damage: A Review

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SUMMARY

An attempt is made to review the problem of therapeutic drug side effects. The magnitude and complexities of the problem are discussed. The functions and difficulties of organisations which deal with the situation in various countries are described. Recommendations are made to improve knowledge about side effects with a view to reducing their incidence. The defects of voluntary notification systems are emphasised and impressions gained from an overseas study tour are presented. The New Zealand scene as viewed during a lecture tour on the subject is also given. The views expressed are those of a practising pathologist who never prescribes drugs, but witnesses the diverse effects of major reactions against the background of the great benefits of modern drug therapy.

INTRODUCTION

Drug therapy in the treatment of disease has expanded explosively in the last 30 years, and it is estimated that thousands of agents are in common use in modern medicine. There is no doubt that lives are saved or prolonged, that incurable conditions are made more comfortable, and that many surgical procedures are avoided by their use. The activities of surgeons have at the same time been made more successful with the control of infection and the advent of a remarkable range of subtle and safe anaesthetic agents. The most dramatic changes in the last three decades have occurred in the control of infections by antibiotics, the treatment of psychological disorders by antidepressants and hypnotics, the relief of pain by a wide range of analgesics, the control of inflammatory and other conditions by steroids, the relief of hypertension by a variety of drugs, and the palliation of neoplastic and other proliferative disorders by immunosuppressive and antimitotic substances.

The extensive use of this great range of agents has brought in its wake a series of undesirable reactions, varying in severity from the trivial and transient to the irreversible and fatal. In a text devoted to the subject (Meyler, Herxheimer, 1968) the 30 authors have referred to no less than 4,700 relevant articles in the medical literature. There is therefore no doubt of the magnitude of the problem, but it has still not yet been fully measured. Detailed assessment continues to be incomplete, and unco-ordinated.

INHIBITORY INFLUENCES

Influences which inhibit research into the problem are exerted unconsciously or deliberately by both prescribers and manufacturers who tend to give undue emphasis to therapeutic advantages and commercial interests when the question of side effects is raised. Unbiased studies have shown that the problem is in general underestimated by the medical and pharmaceutical professions (Inman, 1970; Mansel-Jones, 1970).

Drug manufacturers and their agents inundate doctors daily with a barrage of advertising material which is often presented in a glossy, colourful fashion in which reference to side effects is obscured or underplayed. Some of the techniques used are those which apply in the world of commerce in general (Packard, 1961) and the influence this material exerts on prescribers is not inconsiderable.

Determined efforts to elucidate the possibility of drug damage in specific clinical circumstances are often not made and the conclusion is commonly reached without adequate investigation that the cause of an unexpected syndrome is not the drug therapy. The thalidomide disaster provides a most convincing example of a situation in which numbers of clinicians failed to recognise the cause of a condition, whose incidence was rising dramatically before their eyes (McBride, 1961).

NATIONAL MONITORING SYSTEMS

Assessment of drug damage is not the primary concern of prescribers and manufacturers who direct their interest mainly towards the beneficial effects of particular therapeutic agents. The impact of the occurrence of a significant side effect is therefore delayed by an interval during which the suspected damage is denied or attributed to other causes. The prompt recognition of an adverse reaction depends therefore on the specific activities of personnel other than prescribers and manufacturers. The advent of national organisations to deal with the problem has led to the accumulation of significant information which has alleviated the incidence of untoward reactions, by providing avenues of communication with practising doctors.

The most powerful of these organisations has been the Food and Drugs Administration in the USA which