Summary of Results

Substance	Mol. weight	$\chi \cdot 10^6$		$\chi_{mol} \cdot 10^6$		Difference 10^6	Number of determination **
		calculated	observed	calculated*	observed		
DCM	192,5	−0·68	−0·81 ± 0·01	−131	−155·9 ± 2	25	12
Chloronaphthine	268	−0·68	−0·74 ± 0·02	−181·8	−198·3 ± 5·4	16	8
EMU	254	−0·61	−0·82 ± 0·02	−152·2	−208·3 ± 5·1	56	12
Mercaptopurine	152	−0·46	−0·64 ± 0·02	− 69·7	− 97·3 ± 3	27	8
Myleran	246	−0·55	−0·69 ± 0·02	−135·6	−169·7 ± 4·9	34	8
PEI***	272	−0·40	−0·58 ± 0·02	−110	−157·8 ± 5·4	48	8
TEM	204	−0·61	−0·74 ± 0·02	−123·8	−150·9 ± 4	27	6
Urethane	89	−0·45	−0·64 ± 0·02	− 40·4	− 56·9 ± 1·8	16	10

* The calculated values concern only the contributions given to the suceptibility by atoms and constitutive increments at present known.

** The mean value of more consecutive measurements (usually 6) was calculated as a single determination.

*** Picric acid, for which 3 measurements were carried out, showed the value 20 as difference between calculated and observed susceptibility, parallel to what is observed for PEI. This fact shows that the anomaly observed for PEI is dependent in part on the trinitrophenol ring.

ed hypothesis, concerning the particularly extended electronic orbits could perhaps explain the antineoplastic mechanism of the above mentioned substances, if considered analogous to the interaction between inhibitory and carcinogenic substances[4]. Further, the possible relationship between the extended electronic orbits and the occasional recurring of corresponding regions of higher electronic density, might perhaps also explain the carcinogenic activity of most of the compounds examined.

In conclusion, even considering the anomalies mentioned only from a presumptive point of view, the substances showing antineoplastic activity—as well as those known as carcinogenic—are characterized by anomalies of the electronic cloud inherent with their molecules.

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Sommario

Fu misurata la suscettività diamagnetica di alcune sostanze usate nella chemioterapia dei tumori con lo scopo di confrontare i risultati così ottenuti coi valori della stessa calcolati in base alle sistematiche magnetochimiche. Nei limiti di precisione consentiti dalle conoscenze attuali di queste sistematiche, si è potuto notare una divergenza fra valori osservati e calcolati tale da indurre ad ammettere l'esistenza di anomalie strutturali, precisamente di irregolarità della nube elettronica inerente alle molecole delle sostanze esaminate.

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The Effect of Thyroid Function on the Prothrombin Time Response to Warfarin in Rats*

The coagulation of blood has been reported to be increased in hypothyroid[1] and decreased in hyperthyroid[2] conditions. Although the changes from normal are small, these observations indicate that the level of thyroid function has some effect on the concentration of various coagulation factors. Since indirect anticoagulants of the dicoumarol type act by depressing the synthesis of such factors, their activity in the hypo- and hyperthyroid rat has been investigated. Warfarin (3-[9]α-phenyl-β-acetylethyl[8]-4-hydroxycoumarin), a member of this group of anticoagulants, was used because in the rat it causes a greater and more consistent change of the prothrombin time than dicoumarol.

Male rats, weighing from 175 to 225 g were made hypothyroid by the daily administration in the drinking water of 2 mg of Tapazole (1-methyl-2-mercapto-imidazole)[3] per day, for 8 weeks, and hyperthyroid by the subcutaneous injection of 200 μg of *l*-thyroxin on 4 alternate days. Warfarin[4], at a dose of 500 μg per 100 g of body weight per day was given orally mixed with the feed. Blood samples were taken by tail vein puncture from unanesthetized animals and the prothrombin time determined on whole blood by the method of SCHWAGER and JAQUES[5].

In the hyperthyroid group a statistically significant prolongation of the prothrombin time was found before anticoagulant treatment. The effect of the anticoagulant on the prothrombin time was further significantly increased in the hyperthyroid and significantly decreased in the hypothyroid animals (Table).

The results suggest that in the hypo- and hyperthyroid state the rate of synthesis of factors regulating the prothrombin time is at a level different from normal even if the prothrombin time shows little change. However, the deviation from normal is magnified by the administration of the anticoagulant.

The state of thyroid function has been shown to have an influence on many physiological functions, often in an indirect manner. For example, the increased sympathetic tone or response to adrenaline in the hyperthyroid animal has been stated to be due to a decreased level of amine oxidase, which results in a decreased rate of inactivation of the sympathetic neurohumoral transmitter or administered adrenaline[6].

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Effect of Thyroid Function on Prothrombin Time Response to Warfarin in Rats.

Treatment	Number of Animals	Before Anticoagulant, Prothrombin time, s ± S.E.	First Day on Anticoagulant, Prothrombin time, s ± S.E.	Second Day on Anticoagulant, Prothrombin time, s ± S.E.	Third Day on Anticoagulant, Prothrombin time, s ± S.E.
Normal	10	28·8 ± 1·0	100·0 ± 13·7	190·0 ± 14·5	
Hyperthyroid . . .	10	34·5 ± 1·6*	163·1 ± 17·4*	251·0 ± 19·5**	
Normal	10	31·6 ± 1·3	107·9 ± 7·2	241·1 ± 4·8	424·0 ± 50·0
Hypothyroid . . .	10	34·6 ± 0·7	79·1 ± 6·8*	225·0 ± 7·3	245·0 ± 24·6*

* Difference between means of normal and experimental groups are significant at a probability level $< 0{\cdot}01$.

** Difference between means of normal and experimental groups are significant at a probability level $< 0{\cdot}05$.

The decreased response to the anticoagulant in the hypothyroid state may likewise be due to an increased rate of synthesis or more probably a decreased rate of degradation of prothrombin and other coagulation factors at the cellular level, while the increased metabolic activity in the hyperthyroid state would tend to increase the effect of the anticoagulant by accelerating protein degradation.

Recently, MARTIUS *et al.*[7] have postulated that indirect anticoagulants like dicoumarol may act in a manner similar to thyroxine. Both dicoumarol and thyroxine decrease, while Vitamin K increases, oxidative phosphorylation of mitochondria *in vitro*. The inhibitory activity of coumarin derivatives was found to parallel anticoagulant activity. Dicoumarol has also been shown to inhibit DPNH oxidase activity[8].

These observations are difficult to correlate with the anticoagulant activity of these drugs in the intact animal, where their action is highly specific. Doses which cause a significant decrease of prothrombin levels fail to alter liver functions or change the levels of liver enzymes[9], or cause any other widespread physiological changes one would associate with an uncoupling of oxidative phosphorylation. Hence, while the results demonstrate a synergism between thyroid hormone and indirect anticoagulants, their site or mode of action at the cellular level may not necessarily be identical.

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Zusammenfassung

Die Wirkung von Warfarin, einem Anticoagulans der Dicumarolgruppe, ist erhöht bei hyperthyroiden und vermindert bei hypothyroiden Ratten.

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The Influence of Inorganic Thiophosphate on the Conversion of Parathion to Paraoxon in Rat Liver Slices

As was shown by various authors[1] parathion is converted in the animal body to its oxygen analogue, paraoxon, which is a powerful anticholinesterase; therefore, this metabolic conversion is of primary importance in the toxic action of parathion.

The identity of the enzymic system involved is not clear; the corresponding dehydrogenase seems to be DPN-linked[2]. GAGE[3] suggested that the system may be identical with that of BINKLEY[4] which catalyses the oxidation of inorganic thiophosphate to orthophosphate and perhaps thiosulphate. If this were true, inorganic thiophosphate when present in a sufficiently high concentration should exhibit an inhibitory influence on the conversion of parathion to paraoxon with this system. Examples of such competition of substrates are known even from *in vivo* experiments, e.g. the oxidation of methyl alcohol was found to be retarded by doses of ethyl alcohol[5] etc.

Therefore, the rate of paraoxon formation was followed in female rat liver slices incubated with various concentrations of parathion in the presence of various concentrations of sodium thiophosphate ($Na_2HPSO_3 \cdot 12 H_2O$). The concentrations of the later substance were held within the range that would be innocuous to the experimental animal when injected (the intravenous LD_{50} of the preparation used was 432 mg/kg for female mice and approximately 800 mg/kg for female rats). The incubation was continued until a steady state was reached in which paraoxon was formed as rapidly as it was split by the A-esterase present[6], so that its concentration in the medium did not change. This steady state concentration, which was reached after 60–90 min in the conditions of the experiment, is a measure of the velocity of paraoxon formation, if the rate of this decomposition is supposed to be constant[7]. To be sure that the con-

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