Vitamin $B_{12}$ in Leber und Nieren von verschieden ernährten Ratten

| Nr. | Anzahl von Tieren | Versuchsdiät | Versuchsdauer | Vorherige Diät | Vitamin $B_{21}$ in µg/g | | Relativer Vitamingehalt[3] |
|---|---|---|---|---|---|---|---|
| | | | | | Lebern | Nieren | |
| 1 | 9 | Kontrollen | von Geburt an | – | 0,204 ± 0,016[4] | 1,421 ± 0,032 | 1,95 |
| 2 | 8 | Soya-Mais | von Geburt an | – | 0,022 ± 0,002 | 0,106 ± 0,005 | 0,156 |
| 3 | 8 | Soya-Mais + 3 µg/kg Vit. $B_{12}$ | von Geburt an | – | 0,040 ± 0,004 | 0,182 ± 0,022 | 0,252 |
| 4 | 4 | Soya-Mais + 0,2% jodisiertes Kasein | 1 Woche | Kontrollen | 0,130 ± 0,036 | 1,057 ± 0,150 | 1,56 |
| 5 | 4 | Soya-Mais + 0,1% jodisiertes Kasein | 2 Wochen | Kontrollen | 0,0906 ± 0,017 | 0,304 ± 0,027 | 0,716 |
| 6 | 4 | Soya-Mais + 0,1% jodisiertes Kasein | 3 Wochen | Kontrollen | 0,0760 ± 0,008 | 0,269 ± 0,043 | 0,645 |
| 7 | 4 | Soya-Mais + 0,1% jodisiertes Kasein | 12 Wochen | Soya-Mais | 0,015 ± 0,001 | 0,092 ± 0,006 | 0,177 |
| 8 | 4 | Soya-Mais | 3 Wochen | Kontrollen | 0,127 ± 0,018 | 0,488 ± 0,009 | 0,840 |
| 9 | 4 | Kontrollen | 4 Wochen | Soya-Mais | 0,177 ± 0,022 | 1,129 ± 0,131 | 1,61 |
| 10 | 6 | Soya-Mais + 30 µg/kg Vit. $B_{12}$ | 4 Wochen | Soya-Mais | 0,197 ± 0,029 | 1,594 ± 0,069 | 1,96 |

[3] $\frac{\text{Gesamtmenge von } B_{12} \text{ in Leber + Nieren}}{\text{Körpergewicht}} \times 100.$

[4] Standardfehler des Mittelwertes.

*Summary*

Adult, male rats bred for over 10 generations on a soy meal-corn-diet had vitamin $B_{12}$ values of liver and kidney about 10 times lower than the controls. If the deficient ration was supplemented with 5 µg/kg of $B_{12}$, these values were still about $^1/_5$ of the controls. 3 weeks on the deficient diet lowered the $B_{12}$ levels in the livers and kidneys of previously undepleted rats to about ½, and a similar diet containing 0·1% of iodized casein lowered these levels to about ⅓ of the normal values but did not lower the $B_{12}$-concentration of organs of already deficient rats.

Rats bred on the deficient diet and receiving for 1 month a supplement of 30 µg/kg of vitamin $B_{12}$ or the stock diet with a similar $B_{12}$-content, had normal $B_{12}$-levels in livers and kidneys.

## Magnetochemical Behaviour of some Substances Used in the Medical Treatment of Tumors

In a previous research[1], the magnetochemical behaviour of some carcinogenic substances was examined.

We now considered that the study of the magnetic susceptibility of some chemo-therapeutical substances, of interest for their antineoplastic action, which cannot at present be considered from the standpoint of theoretical chemistry, might be profitable to investigate (at least approximately) in view of the possible presence and type of electronic anomalies.

The following substances were examined:

DMC: di-(2-chloroethyl)-methylamine hydrochloride
Chloronaphthine: di-(2-chloroethyl)-β-naphthylamine
TEM: 2,4,6-triethyleneimino-1,3,5-triazine
PEI: ethyleneimine picrate
EMU: N,N'-dicycloethylenecarbamylhexamethylenediamine
Urethane: ethyl carbamate
Myleran (Mielucin): butyl-1,4-di(methylsulphonate)
6-Mercaptopurine.

Susceptibility measurements were carried out soon after preparation of the substances, because of the lability of the latter. These values were obtained by working with a magnetometric balance of Weiss-Föex type, modified by MAYR[2]. Measurements were related to triply distilled water whose susceptibility ($0{\cdot}72 \times 10^{-6}$) had been previously controlled by comparative measurements with doubly distilled mercury. Temperature 20–22° C.

The susceptibility calculations were carried out according to the magnetochemical systematology of PACAULT[3] based on PASCAL's experimental data. The values calculated in this way are based on the contribution to diamagnetism of single atoms (atomic susceptibility) and bonds between atoms of the same molecule (constitutive increments). These values are, in many cases so far considered, in agreement with the experimental results within a limit of 2%. Discordant values occur when the constitutive increments are not yet known with sufficient precision; in these cases the calculated values must be considered as indicative data; and such discordance may be a useful indication for the detection of constitutional characteristics still unknown.

Calculated and experimental data are tabulated.

They show, as a general characteristic, that the experimental values are superior to the calculated ones; the hypothesis is therefore advanced that in these substances one or more π-electrons are spread on the adjacent atoms. In a later paper, one of us (MAYR) will discuss from the theoretical standpoint the admissibility of this assumption and the possibility of a relationship between particularly extended orbits and corresponding regions of greater electronic rarefaction, occasionally coexisting, however, with centers of higher electronic density.

Without venturing to explain a phenomenon which is still rather complex, it may be thought that the advanc-

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[2] G. MAYR, R. C. Ist. Lombardo Sci. Lett. *83*, 3 (1950).

[3] A. PACAULT, Rev. Sci. *86*, no. 3288, p. 38 (1948).

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.

[4] H. C. Crabtree, Cancer Research *5*, 351 (1945).

## 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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