found to have a comparable high potency on PCPA- and on benzoquinolizine-induced PGO waves[7]. Like 5-HTP and the dihydrogenated ergots, LSD-25[12] and CF 25-397[13] are able to shorten paradoxical sleep in the rat. Neurochemical and neurophysiological effects consistent with a central tryptamine-like action of LSD-25 and PTR 17-402 have been reported earlier[14-16], whereas data on CF 25-397 will be published[13,17]. In addition, these compounds are known to possess dopamine receptor stimulant properties as well[18-20]. Compared to LSD-25, methysergide was considerably weaker in decreasing reserpine-induced PGO waves. This finding confirms earlier observations.

Bromocriptine had the weakest inhibitory effect on reserpineinduced PGO waves of all ergot derivatives investigated. At lower doses, bromocriptine and CM 29-712 even tended to increase the number of PGO waves. Bromocriptine and CM 29-712 are known as dopamine receptor stimulants without direct actions on serotonin receptors[13].

When surveying our results with ergot derivatives, it appears that the most potent inhibitors of PGO waves - LSD-25, PTR 17-402, CF 25-397 - are potent agonists at central serotonin and dopamine receptor sites. In comparison, dihydrogenated compounds, which were less potent inhibitors of PGO waves, induce, apart from their serotonin-like action, a weaker dopamine receptor stimulation. Finally, the dopamine receptor stimulants CM 29-712 and bromocriptine were the least potent in reducing PGO waves.

Several authors have proposed that PGO wave activity is under the inhibitory control of serotoninergic neurones in the pontine reticular formation[3,21,22]. Our results are in agreement with the hypothesis that ergot derivatives exert their inhibitory action on reserpine-induced PGO waves by stimulating such serotonin receptor sites. However, the differences in potencies observed suggested that, in addition, dopaminergic stimulation might be involved. Indeed, the ability of ergot derivatives to counteract reserpine-induced akinesia has been ascribed to stimulation of striatal dopamine receptors[13,23]. Furthermore, an inhibitory pathway descending from the striate nucleus to the pontine region[24] has been described which might be involved in the inhibitory effect of bromocriptine on morphineinduced analgesia[9,13,25]. Therefore it is suggested that part of the inhibition by ergot derivatives of reserpine-induced PGO waves is brought by stimulation of striatal dopamine receptors.

12 H. Depoortere and D.M. Loew, Brt. J. Pharmac. *41*, 402P (1971).
13 J.M. Vigouret, H.R. Bürki, A.L. Jaton, P.E. Züger and D.M. Loew, Pharmacology *16*, suppl. 1, 156 (1978).
14 G.K. Aghajanian, H.J. Haigler and F.E. Bloom, Life sci. *11*, 615 (1972).
15 N.E. Andén, H. Corrodi, K. Fuxe and T. Hoekfelt, Brt. J. Pharmac. *34*, 1 (1968).
16 H. Corrodi, L.O. Farnebo, K. Fuxe and B. Hamberger, Eur. J. Pharmac. *30*, 172 (1975).
17 K. Fuxe, B.B. Fredholm, L.F. Agnati, S.O. Oegren, B.J. Everitt, G. Jonsson and J.Å. Gustafsson, Pharmacology *16*, suppl. 1, 99 (1978).
18 L. Pieri, M. Pieri and W. Haefely, Nature *252*, 586 (1974).
19 K. Fuxe, L.F. Agnati, T. Hoekfelt, G. Jonsson, P. Lidbrink, A. Ljungdahl, A. Lofstrom and U. Ungerstedt, J. Pharamc. (Paris) *6*, 117 (1975).
20 A.L. Jaton, D.M. Loew and J.M. Vigouret, Brt. J. Pharmac. *56*, 371P (1976).
21 M. Jouvet, Ergebn. Physiol. *64*, 166 (1972).
22 M.A. Ruch-Monachon, M. Jalfre and W. Haefely, Archs int. Pharmacodyn. *219*, 326 (1976).
23 A.M. Johnson, D.M. Loew and J.M. Vigouret, Br. J. Pharmac. *56*, 59 (1976).
24 D. Albe-Fessard, in: Proceedings of the third International Pharmacology Meeting, Pharmacology of Pain, vol. 9, p. 131. Ed. Lim, Armstrong and Pardo, Pergamon Press, Oxford 1968.
25 D.M. Loew, J.M. Vigouret and A.L. Jaton, Post-grad. Med. J. *52*, suppl. 1, 40 (1976).

Cytostatic activity of organic compounds and their average quasi-valence number

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Summary. It is found that the average quasi-valence numbers of alkylating cytostatics lie in the region of potential carcinogens, while the average quasi-valence numbers of antimetabolites predominantly cover the region of noncarcinogens. Implications of this finding on the design of new drugs are discussed.

Material and methods. The potential of electron-ion interaction[1] has been calculated for a large number of organic compounds and related to their biological effects in mammals[2]. On the basis of this work, a simple theoretical criterion of chemical carcinogenicity has been developed[3]. It is shown that the average quasi-valence number (the ratio of the sum of all atomic valence electrons[4] and the number of atoms in the molecule) for potential carcinogens is lower than 3.20, while the average quasi-valence numbers of noncarcinogens exceed the borderline value of 3.20.

Further analysis[5] has disclosed the correlation between the types of carcinoma and the average quasi-valence number in case of 110 carcinogenic substances thorougly evaluated by Lyon experts[6]. Organic compounds, depending on their average quasi-valence numbers, can cause different types of carcinoma in mammals. This reveals specific biological activity of chemical compounds in vivo.

On the basis of the above findings, one might expect that different drugs used for curing the same illness(es) should have similar or rather close average quasi-valence numbers. The preliminary data on antibiotics, hormones, psychopharmaceuticals and some other classes of organic substances have shown that this is indeed the case.

Results and discussion. Results of the average quasi-valence number calculation in the case of 105 alkylating organic compounds investigated by A. Golding and H.B. Wood, Jr, of the USA National Cancer Institute[7], are presented in the figure.

Most alkylating substances (95%), characterized by average quasi-valence numbers lower than 3.20, cover the region of potential carcinogens. Only in 5 cases do the corresponding average quasi-valence numbers exceed the borderline of noncarcinogenicity (3.20).

All alkylating substances (mainly belonging to different nitrogen mustards) producing 50% or higher increase in the life span in systemic leukemia L1210, have average quasi-valence numbers below the value of 3.20. Similar results are obtained for alkylating agents-antitumour drugs used in clinical practice. A survey of such agents[8] is given in table 1. Only one drug out of 24 has a higher average quasi-

Table 1. Alkylating cytostatics and average quasi-valence number Z*

Chemical name	Proprietary or other name	Empirical formula	Z*
1,6-bis(2-Chloroethylamino)-1,6-dideoxy-D-mannitol	Degranol, R-2, BCM, Mannomustine	$C_{10}H_{22}N_2O_4Cl_2$	2.45
1,6-bis(2-Bromoethylamino)-1,6-dideoxy-D-mannitol	Bromodegranol, R-13	$C_{10}H_{22}N_2O_4Br_2$	2.45
1,6-bis(2-Methanesulphonyloxyethyl-amino)1,6-dideoxy-D-mannitol	Mesyldegranol, R-49	$C_{12}H_{28}N_2O_{10}S_2$	2.93
1,6-Dimethanesulphonyl-D-mannitol	Mannogranol, R-37, Mannitomyleran	$C_8H_{10}O_{18}S_2$	3.20
1,2,5,6-Tetramethanesulphonyl-D-mannitol	Tetramesylmannitol, R-52	$C_{10}H_{21}O_{14}S_4$	3.45
1,4-bis(2'-Methanesulphonyloxyethyl-amino)1,4-dideoxy-meso-erythritol	Erythritol derivative, R-74	$C_{10}H_{24}O_8N_2S_2$	2.91
1,6-Dibromo-1,6-dideoxy-dulcitol	Dibromodulcitol, DBD	$C_6H_{12}O_4Br_2$	2.58
1,6-Dibromo-1,6-dideoxy-D-mannitol	Myelobromol, Dibromomannitol	$C_6H_{12}O_4Br_2$	2.58
Tris(2-Chloroethyl)amine	tris-Nitrogen mustard	$C_6H_{12}NCl_3$	2.00
N,N-bis(2-Chloroethyl)p-aminophenyl-buturic acid	Leukeran, Chlorambucil, Chloraminophene, Ecloril	$C_{14}H_{19}NO_2Cl_2$	2.47
Methyl-bis(2-chloroethyl)amine	Embichin, Nitrogen mustard	$C_5H_{11}NCl_2$	2.00
2-Chloropropyl-bis(2-chloroethyl)-amine	Novembichin	$C_7H_{14}NCl_3$	2.00
N,N-bis(2-Chloroethyl)p-amino-phenylalanine	L-Sarcolysin, Melphalan, PAM, Sarcoclorin	$C_{13}H_{18}N_2O_2Cl_2$	2.54
6-Methyl-5-/bis(2-chloroethyl)-amino/-uracil	Dopan	$C_9H_{13}N_3O_2Cl_2$	2.69
Methyl-bis(2-chloroethyl)amine N-oxide	Nitromin, Mitomen, Nitrogen mustard N-oxide	$C_5H_{11}NOCl_2$	2.20
N,N-bis(2-Chloroethyl)N'O-propylene-phosphoric acid ester diamide	Endoxan, Cyclophosphamide, B-518, Cytoxan	$C_7H_{15}N_2O_2PCl_2$	2.48
1,4-bis(Methanesulphonyloxy)butane	Myleran, Busulphan	$C_6H_{14}O_6S_2$	3.07
2,4,6-tris(Ethylenimino)-1,3,5-triazine	Triethylene melamine, TEM	$C_9H_{12}N_6$	2.89
Triethylenephosphoramide	TEPA	$C_6H_{12}N_3PO$	2.70
Triethylenethiophosphoramide	Thio-TEPA	$C_6H_{12}N_3PS$	2.70
2,3,5-tris(Ethyleneimino)-1,4-benzoquinone	Treonimon	$C_{12}H_{13}N_3O_2$	2.93
2,5-bis(Ethyleneimino)-3,6-dipropoxy-1,4-benzoquinone	E-39, Inproquone	$C_{16}H_{22}N_2O_4$	2.73
2,5-bis(Ethyleneimino)-3,6-bis(methoxy-ethoxy)-1,4-benzoquinone	A-139	$C_{16}H_{22}N_2O_6$	2.87
1,3-bis(2-Chloroethyl)-1-nitrosourea	BCNU	$C_5H_9N_3O_2Cl_2$	2.76

* Structural formulae can be found in Sellei et al.[8].

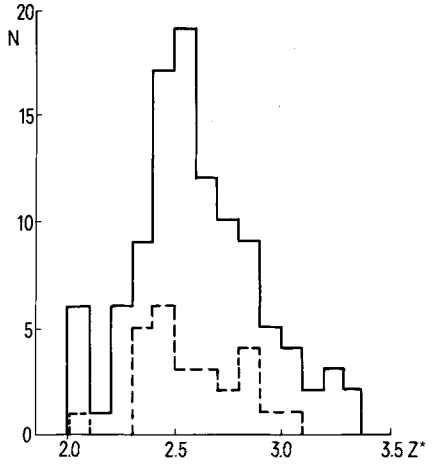
Table 2. Antimetabolic cytostatics and average quasi-valence number Z*

Chemical name	Proprietary or other name	Empirical formula	Z*
4-Aminopteroylglutamic acid	Aminopterin	$C_{19}H_{20}N_8O_5$	3.19
4-Amino-N^{10}-methyl pteroylglutamic acid	Methotrexate	$C_{20}H_{22}N_8O_5$	3.13
2,4-Diaminopyrimidine	Daraprim	$C_4H_6N_4$	3.00
6-Mercaptopurine	Purinethol	$C_5H_4N_4S$	3.57
8-Azaguanine	8-Azaguanine	$C_4H_4N_6O$	3.73
5-Fluorouracil	5-FU	$C_4H_3N_2O_2F$	3.50
5-Fluoro-2'-deoxyuridine	5-FUDR	$C_9H_{11}N_2O_5F$	3.14
6-Azauridine	AzUr	$C_8H_{11}N_3O_6$	3.36
0-Diazoacetyl-L-serine	Azaserine	$C_5H_7N_3O_4$	3.47
6-Diazo-5-oxo-L-norleucine	DON	$C_6H_9N_3O_3$	3.14

* Structural formulae can be found in Sellei et al.[8].

valence number than 3.20. On the other side, antimetabolites[8] are generally characterized by higher average quasi-valence numbers, close to or above the borderline value of 3.20, as can be seen from table 2.

The fact that 'Carcinogenic substances have also a paradoxical tumour-inhibitory action' (Sellei et al.[8], p. 197) according to the valence theory does not seem paradoxical. Alkylating cytostatics, which have average quasi-valence numbers below 3.20, should be treated as potential carcinogens, while the antimetabolic cytostatics generally should belong to the class of noncarcinogens. The action of alkylating cytostatics could be coupled with their potential carcinogenic activity, while the mechanism of the antimetabolic cytostatics might be of another type.



Number of investigated alkylating compounds vs. average quasi-valence number (full line - all investigated compounds, dashed line - compounds having good activity).

The average quasi-valence number criterion could be used for the selection of cytostatics of the above-mentioned 2 groups of substances. As can be seen from the figure, optimal antitumour action can be expected in the given group of substances only for alkylating cytostatics having some specific average quasi-valence numbers (2.3-2.9). Selection and 'design' of new alkylating cytostatics could, in this way, be guided by the choice of the proper average quasi-valence number.

We believe that the valence theory could be of benefit to the selection of alkylating compounds having good cytostatic activity, and that it might shed additional light on the problem of cytostatic action.

1 V. Veljković and D.I. Lalović, Phys. Lett. *45A*, 59 (1973).
2 V. Veljković and D.I. Lalović, Cancer Biochem. Biophys. *1*, 295 (1976).
3 V. Veljković and D.I. Lalović, Experientia *33*, 1228 (1977).
4 In case of halogen elements instead of Z = 7, Z = 1 should be taken.
5 V. Veljković (to be published).
6 IARC Monographs 'Evaluation of Carcinogenic Risk', vol. 1-8. Lyon 1972-1975.
7 A. Goldin and H.B. Wood, Jr, Ann. N.Y. Acad. Sci. *163*, 589 (1969).
8 C. Sellei, S. Eckhardt and L. Németh, Chemotherapy of Neoplastic Diseases. Akadémia Kiadé, Budapest 1970.

Effect of variations in temperature on antimuscarinic activity in guinea-pig atria[1]

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Summary. The characteristics of the antimuscarinic activity of homatropine, gallamine and stercuronium in guinea-pig atria remained constant over the temperature range 22–37 °C in that a linear Arunlakshana-Schild plot was obtained with homatropine and nonlinear plots occurred with gallamine or stercuronium. A trend towards higher dose-ratios with reduction in temperature was only significant for gallamine.

Reduction of temperature causes marked changes in the interaction of atrial adrenoceptors with agonists and antagonists. There is an interconversion of β-adrenoceptors to the α-type[2,3], an increase in sensitivity to sympathomimetics[4,5] and partial agonists develop characteristics of full agonists[6]. The affinity of β-adrenoceptor antagonists in the atria may be decreased[3,7] or unaltered[4,5].

In contrast, the effect of temperature on caridia muscarinic receptors has been little investigated. Benfey[8] found that phenoxybenzamine was a less active antagonist of acetylcholine at 14 °C than at 24 °C in frog heart whereas atropine was equieffective at both temperatures. A decrease in effectiveness is also observed with phenoxybenzamine in guinea-pig atria on lowering the temperature from 31 to 14 °C[8] although the response to acetylcholine in this tissue is almost unchanged with a decrease from 32 to 18 °C[9].

Cardiac muscarinic receptors are selectively inhibited by gallamine[10,11] and the antimuscarinic action of gallamine can be differentiated from that produced by atropine in a number of ways[13]. For example, although gallamine produces parallel shifts of the concentration-response curve for the negative inotropic response to carbachol (CCh) in guinea-pig atria the degree of antagonism reaches a limiting value at high concentrations of gallamine resulting in an Arunlakshana-Schild (A-S) plot[12], which is nonlinear[13]. An allosteric mechanism was proposed to account for the antimuscarinic activity of gallamine.

An investigation of the effect of temperature on the interaction of gallamine and homatropine was undertaken to determine whether differences occur in the nature and extent of the blockade produced by the 2 antagonists with variations in temperature from 22 to 37 °C. Homatropine was chosen in preference to atropine because the former can be used over the same concentration range as that required to demonstrate the antimuscarinic activity of gallamine and the resulting nonlinear A-S plot.

Methods. Left atria of guinea-pigs in McEwen's solution[14] gassed with O_2/CO_2 (95:5) were stimulated electrically at 1.8 or 3 Hz with pulses of 2 msec duration and supramaximal voltage at 22, 25, 32 or 37 °C (±0.5 °C). At 22 °C atria were stimulated at 1.8 Hz as arrhythmias developed with stimulation at 3 Hz. Concentration-response lines to CCh were determined in the absence and presence of antagonists as described previously[13] except that the contact time for CCh was increased up to 8 min in some experiments at the lower temperatures to ensure full development of the response. Statistical comparisons were made using Student's t-test (2 tailed).