NaF alone had a 24 h oral $LC_{50}$ of 0.14% (Figure 1). To test for antagonism, 0.4% NaF, which generally gives 100% mortality when offered alone, was fed to the houseflies admixed with various amounts of NaCl, NaCNS and NaI. The results, from which strong antagonism is evident, are presented in the Table. Though the order of effective protection was NaCNS > NaI > NaCl, there seemed to be no substantial difference between the three antagonists; this became even clearer when the results of the Table were plotted on probit/log.-conc. paper. However, when the concentrations are expressed in moles (Figure 2) instead of in percentages, the difference between the three salts becomes more pronounced: on a molar basis, NaI was a more effective protectant than NaCNS, and NaCl was again the poorest antagonist. Essentially the same results were obtained with KCNS, KCl and KI as NaF-antagonists. NaBr showed an only negligible detoxifying action for NaF.

The results of this study throw some light on the interesting finding that the tempering of fish to chloride somewhat reduced their susceptibility to subsequent exposure to fluoride[8].

*Zusammenfassung.* Zufügung von NaCNS-, NaI- oder NaCl-Überschuss zu NaF-Lösungen entgiftet letztere für die Hausfliege.

K. R. S. Ascher and Gerta Rones[9]

*Department of Toxicology, Volcani Institute of Agricultural Research, Beit-Dagan, Rehovot (Israel), February 19, 1965.*

[8] J. M. Neuhold and W. F. Sigler, Trans. Am. Fisheries Soc. *89*, 4 (1960); Science *135*, 732 (1962).

[9] Contribution No. 839-E, 1965 Series, from the National and University Institute of Agriculture, Rehovot (Israel).

## The Relationship Between Blood Cholinesterase Activity and Neoplastic Diseases

In earlier investigations we found that blood cholinesterase activity was increased in asthmatic patients. Later, during further studies, we proved that ACTH[1,2] and corticosterone[3] produced increased cholinesterase activity ($P < 0.001$) and that adrenalectomized rats[4] showed diminished cholinesterase activity in plasma, whole blood and blood cells which was also highly significant statistically ($P < 0.001$).

In our present investigation we determined cholinesterase activity in plasma, whole blood and blood cells in 22 adult male patients suffering from neoplastic diseases in different locations. Determinations were also made on 16 adult females suffering from the same disease. The diagnosis of malignant tumour was made by histological study of the biopsies.

Cholinesterase activity in plasma, whole blood and blood cells was also determined in 23 adult males and 20 adult female subjects, all apparently healthy, who were used as controls.

We used the Biggs et al.[5] colorimetric method for these determinations.

The findings in the male patients were compared with those of the controls of the same sex, and it was proved that there was pronounced diminution in cholinesterase activity values in plasma, whole blood and blood cells in the patients. Statistical analysis showed highly significant differences ($P < 0.001$) (Table I).

This same phenomenon was found in the females suffering from cancer; there was accentuated diminution of cholinesterase activity in plasma, whole blood and blood cells. Statistical analysis, carried out using the normal female subjects as controls, also showed highly significant differences ($P < 0.001$) in plasma, whole blood and blood cells (Table II).

There were diminished values in cholinesterase activity in all the patients in comparison with the normal values for each sex. This fact, by its constancy, can be used as an element for presumptive diagnosis of a neoplastic disease.

We have been unable to find any relationship between our earlier investigations on cholinesterase activity and

[1] J. R. Vaccarezza and L. Peltz, Presse Méd. *68*, 723 (1960).

[2] J. R. Vaccarezza and J. A. Willson, Exper. *20*, 23 (1964).

[3] J. R. Vaccarezza and J. A. Willson, Exper. *20*, 425 (1964).

[4] J. R. Vaccarezza and J. A. Willson, Exper. *21*, 205 (1965).

[5] H. G. Biggs, S. Carey, and D. B. Morrinson, Am. J. clin. Path. *30*, 181 (1958).

Table I. Units of cholinesterase activity found in normal adult males and in those suffering from neoplastic diseases

| | Plasma | | Whole blood | | Blood cells | |
|---|---|---|---|---|---|---|
| | Normal ♂ | Cancer ♂ | Normal ♂ | Cancer ♂ | Normal ♂ | Cancer ♂ |
| Average UCh activity | 109 | 76 | 170 | 115 | 239 | 170 |
| Standard deviation | ± 9.3 | ± 15.8 | ± 11.5 | ± 19.0 | ± 19.0 | ± 24.9 |
| Standard error | ± 1.9 | ± 3.3[a] | ± 2.4 | ± 4.0[b] | ± 3.9 | ± 5.2[c] |
| Number of cases | 23 | 22 | 23 | 22 | 23 | 22 |

[a] $P < 0.001$. [b] $P < 0.001$. [c] $P < 0.001$.

Table II. Units of cholinesterase activity found in normal adult females and in those suffering from neoplastic diseases

| | Plasma | | Whole blood | | Blood cells | |
|---|---|---|---|---|---|---|
| | Normal ♀ | Cancer ♀ | Normal ♀ | Cancer ♀ | Normal ♀ | Cancer ♀ |
| Average UCh activity | 94 | 68 | 139 | 105 | 200 | 161 |
| Standard deviation | ± 10.5 | ± 5.4 | ± 8.7 | ± 10.3 | ± 13.1 | ± 13.3 |
| Standard error | ± 2.3 | ± 1.3[a] | ± 1.9 | ± 2.5[b] | ± 2.9 | ± 3.3[c] |
| Number of cases | 20 | 16 | 20 | 16 | 20 | 16 |

[a] $P < 0.001$. [b] $P < 0.001$. [c] $P < 0.001$.

the suprarenal function and our present investigation, because up to the present there is no proof of diminution of the corticosuprarenal function in neoplastic diseases. On the contrary, in certain types of tumours, the suprarenal function is increased[6] and, according to other authors, cortisol metabolism is also changed[7]. In any case, it is fairly probable that the mechanism that produces the fall in cholinesterase activity in cancer is not in any way related to the suprarenal hormones; it is possible that other factors as yet unknown play a part in this. There is also a difference in the diminution of cholinesterase activity caused by the suppression of adrenal hormones, and the diminution found in neoplastic diseases. In the first case, the greatest diminution is found in the fraction corresponding to the blood cells, the variation in plasma being much less. The diminution of cholinesterase activity in neoplastic diseases is more homogenous, because both the plasma and cell fractions are intensely diminished.

*Résumé.* On a étudié l'activité cholinestérasique dans le plasma, le sang total et les cellules sanguines chez 23 adultes de sexe masculin et chez 20 adultes de sexe féminin apparemment sains, et dans les mêmes fractions, chez 22 hommes adultes et chez 16 femmes adultes, malades du cancer. On a constaté une diminution très marquée de l'activité cholinestérasique dans le plasma, le sang total et les cellules sanguines chez tous les malades. La différence a été hautement significative ($P < 0{,}001$). Cette détermination peut avoir une valeur présomptive dans le diagnostic du cancer.

J. R. VACCAREZZA and J. A. WILLSON

*Laboratorio de Investigaciónes Fisiopatológicas, Paraná 981, Buenos Aires (Argentina), and Laboratorio Central del Hospital Muñiz, January 13, 1965.*

[6] H. J. WETSTONE, R. V. LAMOTTA, A. BELLUCCI, R. TENNANT, and B. V. WHITE, Am. J. int. Med. *52*, 102 (1960).
[7] E. E. WERK, L. J. SHOLLITON, and R. T. MARNELL, Am. J. Med. *34*, 192 (1963).

## Regional changes of the Cholinergic System in the Guinea-Pig's Brain after Physostigmine

It is well known that cholinesterase inhibitors (ChEI) desynchronize the EEG[1,2]; however, the activation is limited to the cortical areas[3,4]. Moreover, the ChEI cause dissociation between behaviour[5] and ACh content of the brain: the signs of excitatory state are associated with increased ACh levels which are, instead, characteristic of reduced nervous activity[6,7].

To obtain further information on the central effects of physostigmine, we studied the changes the drug produced in the cholinergic systems in the different areas of the guinea-pig's brain.

*Methods.* Physostigmine sulphate was given i.p. to guinea-pigs of both sexes weighing 250–350 g. The animals were decapitated 20 min, 1 h, and 3 h after 0.2–1 mg/kg and, as soon as convulsions developed (20–30 min), after 5 mg/kg. Different areas of the brain (see Tables) were quickly removed and submitted to the extraction procedure[8] and the ACh content was bio-assayed on the eserinized frog's rectus muscle.

Other animals were treated for a week with physostigmine 100 $\gamma$/kg i.p. 24 h after the 7th injection the animals were killed to determine (a) the ACh content; (b) cholinoacetylase activity (ChA), according to the method of BULL et al.[9] at 37°C; (c) total cholinesterase activity (ChE), according to AMMON's method[10], as described by AUGUSTINSSON[11] at 37°C.

*Results.* Normal values of total ACh, ChE, ChA are reported in Table I. We also calculated (a) the minimum theoretical time required to synthesize (ST) and hydrolise (HT) the total amount of transmitter present in a given

[1] E. K. KILLAM, Pharmacol. Rev. *14*, 175 (1962).
[2] C. LOEB, F. MAGNI, and G. F. ROSSI, Arch. ital. Biol. *98*, 294 (1960).
[3] M. MONNIER and W. ROMANOWSKY, Electroenceph. clin. Neurophysiol. *14*, 486 (1962).
[4] C. SERGIO and V. G. LONGO, in *Neuropsychopharmacology*. Proceedings of the 1st International Congress of Neuropsychopharmacology, Roma (1958) (Elsevier Publ. Co., 1959), p. 411.
[5] P. B. BRADLEY and A. N. NICHOLSON, Electroenceph. clin. Neurophysiol. *14*, 824 (1962).
[6] W. FELDBERG, Arch. int. Physiol. *59*, 544 (1951).
[7] F. CROSSLAND, J. Pharm. Pharmacol. *12*, 1 (1960).
[8] L. BEANI and C. BIANCHI, J. Pharm. Pharmacol. *15*, 281 (1963).
[9] G. BULL, C. D. HEBB, and D. RATKOVIC, Biochem. biophys. Acta *67*, 138 (1963).
[10] R. AMMON, Pflügers Arch. ges. Physiol. *233*, 486 (1934).
[11] K. B. AUGUSTINSSON, Acta physiol. scand., Suppl. *15*, 52 (1948).