not present in detectable amounts in the blood serum of the majority of neonates, although mononuclear cells, including those adherent to plastic, are able to produce this factor and, to a certain degree, to respond to induction by bacterial products. Considerable TNF activity was found in the serum of some infants, evidently due to intrauterine activation of the TNF-producing cells. It is important to discover to what extent the presence of TNF in the serum reflects pathological conditions arising during hyperstimulation of macrophages. In these children, in the case of infection, there may perhaps be a high degree of disk of onset of systemic release of TNF, giving rise to physiological decomposition, tissue damage, and lethal shock.

The mononuclear cells of newborn infants can thus produce TNF, but TNF activity cannot be found in serum from the cord blood of the majority of healthy infants.

LITERATURE CITED

1. B. Beutler, J. W. Milsark, and A. Cerami, Science, 229, 869 (1985).
2. A. Biondi, G. Poli, C. Parravicini, et al., Immunology of the Neonate, ed. by G. R. Burgio et al., New York (1987), pp. 59-66.
3. G. Bismuth, M. Duphot, and J. Theze, J. Immunol., 134, 1415 (1983).
4. A. Boyum, Scand. J. Clin. Lab. Invest., 21, Suppl., 97, 77 (1968).
5. A. Cerami and B. Beutler, Immunol. Today, 9, 28 (1988).
6. T. Decker, M.-L. Lohmann-Matthes, and G. E. Gifford, J. Immunol., 138, 957 (1987).
7. V. E. Kelley, W. Fiers, and T. B. Strom, J. Immunol., 132, 240 (1984).
8. D. N. Mannel, Immunobiology, 172, 283 (1986).
9. K. Pfizenmaier, P. Scheurich, C. Schluter, and M. Kronke, J. Immunol., 138, 975 (1987).

ANALYSIS OF CORRELATION BETWEEN KINETICS OF BLOOD SERUM CHEMILUMINESCENCE AND EXPERIMENTAL TUMOR GROWTH

V. A. Baraboi and V. É. Orel

UDC 616-006-092:612.117.5.014.445

KEY WORDS: spontaneous chemiluminescence; antioxidants; tumor growth; carcinogenesis.

One of the particular metabolic features of a growing tumor is its accumulation of bio-antioxidants [7], which stimulate tumor growth by inhibiting free-radical oxidation (FRO) [4]. One manifestation of interaction between host and tumor [9] is the correlation between free-radical oxidation and antioxidative activity in the body media during tumor growth, an appropriate indicator of which is the kinetics of spontaneous chemiluminescence (SCL) [1, 2, 14], and the most convenient object for investigation is blood serum (plasma). The view has developed in the literature that reduction of the intensity of luminescence, as a result of "pumping over" of antioxidants from the tissues into the developing tumor, is characteristic both of tumor tissue and of blood [6, 13].

Our experimental and clinical data indicate a different, and even opposite, effect of tumor processes of different nature on the kinetics of SCL of blood serum [2, 3, 12, 14]. However, there has been no attempt to analyze the correlation which we found between the kinetics of SCL and the kinetics of tumor growth. The investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

The intensity of SCL of the blood serum was determined on an original apparatus based on the FÉU-39a photoelectronic multiplier [14]. After rapid decapitation of the animals their blood was centrifuged at 1500 rpm for 10 min. Samples of serum, 1.5 ml in volume,

---

Kiev Research Roentgenoradiologic and Oncologic Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR M. G. Shandala.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 2, pp. 224-226, February, 1989. Original article submitted December 18, 1987.

0007-4888/89/0002-0240$12.50

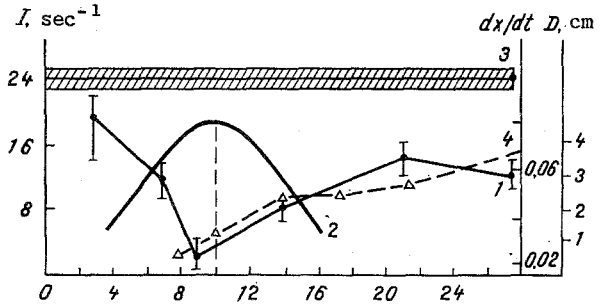

Fig. 1

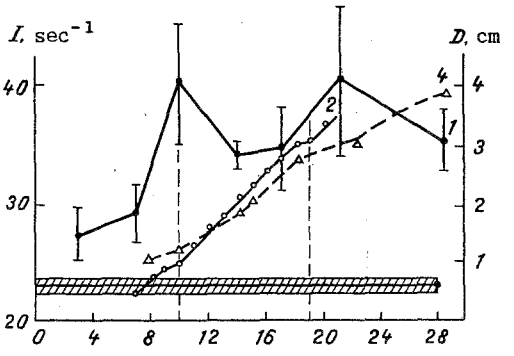

Fig. 2

Fig. 1. SCL of blood serum and rate of growth of rat sarcoma 45. 1) Serum SCL of rats with sarcoma 45; 2) kinetics of growth of sarcoma 45 [11]; 3) SCL in control 4) kinetics of change in mean diameter of sarcoma 45. Here and in Figs. 2 and 3: abscissa, time (in days).

Fig. 2. Serum SCL and rate of growth of Guérin's carcinoma. 1) Serum SCL of rats with Guérin's carcinoma; 2) kinetics of change in mean diameters of tumor [11]; 3) SCL in control; 4) kinetics of change in mean diameters of tumor.

were immersed in a dark glass bottle in a cuvette, with a bottom made of optical quartz, for measurements of SCL at 38.0 ± 0.1°C.

Experiments were carried out on 393 male laboratory rats and 100 BALB/c mice. Tumor cells were transplanted into the rats by subcutaneous injection of 0.5 ml of a 10% suspension of them into the region of the right thigh. A "regressor" model with Moloney virus, as well as injection of Rauscher virus were carried out on BALB/c mice by N. L. Novichenko. Induction of carcinogenesis in the rats by giving 10 intratracheal injections of 3,4-benz(a)-pyrene at intervals of 7 days in total doses of 0.1, 5, and 25 mg per rat was undertaken by T. N. Yurkovskaya. The kinetics of growth of the tumor was estimated from its average diameters, in millimeters, and the change in the mean increase in volume in the present experiments, and by using data obtained by Émanuél' [15].

EXPERIMENTAL RESULTS

Growth of transplanted sarcoma 45 and Walker's carcinosarcoma of rats, induced by Moloney and Rauscher mouse tumor viruses, and carcinogenesis induced by injection of 3,4-benz(a)pyrene and DMBA, were accompanied by a regular and more or less profound decrease in the intensity of SCL of the blood serum. Meanwhile growth of transplated Guérin's carcinoma, Pliss' lymphosarcoma, and Svec's erythromyelosis, and carcinogenesis induced by injection of diethylnitrosamine (DENA) into rats were accompanied by an equally regular increase in the intensity of serum SCL. Maximal deviations of the intensity of SCL from the initial level coincided as a rule in time with the period of maximal rate of growth of the tumor.

Comparison of the kinetics of the serum SCL of the rats and the rate of growth of sarcoma 45 (Fig. 1) reveals its antibathic character; the minimum of intensity of SCL corresponds to the maximum of rate of tumor growth.

Growth of Guérin's carcinoma (Fig. 2) was accompanied by an increase in the intensity of the serum SCL [1]. Two peaks of intensity of SCL described, namely on the 10th (+43%) and 21st days (+42.5%), correspond to points of inflection of the curve of growth of the mean diameters of the tumor (our own data and [15]).

The curve of serum SCL of rats with Pliss' lymphosarcoma was characterized by the presence of a peak (+30%) which coincided with the beginning of the period of growth of the mean diameters of the tumor; subsequently the curve became linear (Fig. 3). Comparative analysis of correlation between maximal amplitude of fluctuations of serum SCL and maximal relative rate of tumor growth for these strains (sarcoma 45, Guérin's carcinoma, Pliss' lymphosarcoma) confirmed the existence of close correlation (0.90-0.93) between these parameters.

Comparison of the kinetics of tumor growth [15] and the kinetics of the change in serum SCL of rats with erythromyelosis and Walker's carcinosarcoma (Fig. 3) also indicates that the point of inflection of the curve of mean tumor diameters (5th and 11th days for these strains)

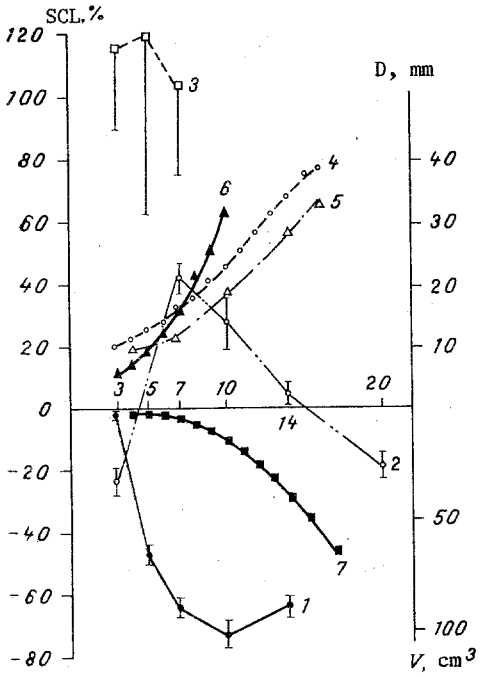

Fig. 3. Serum SCL and rate of growth of Walker's carcinosarcoma, Pliss' lymphosarcoma, and Svec's erythromyelosis of rats. 1, 2, and 3) Serum SCL of rats with Walker's carcinosarcoma, Pliss' lymphosarcoma, and Svec's erythromyelosis; 4-7) kinetics of change in mean diameters of Pliss' lymphosarcoma (our own data), Svec's erythromyelosis, and Walter's carcinosarcoma, respectively.

corresponds to maximal deviation of intensity of SCL – by 120 and 75%, respectively.

Tumor growth induced in BALB/c mice by Moloney virus is accompanied by a significant decrease in the intensity of SCL, corresponding to the stage of tumor growth. The period of progression of the tumor [8] corresponds to a fall of SCL with a minimum on the 12th day. In the stage of tumor regression, the intensity of SCL in the blood serum gradually rises. Carcinogenesis induced by Rauscher virus also reduces SCL in the stage of tumor growth.

On the 4th day after the last injection of 3,4-benz(a)pyrene, a dose-dependent decrease in the intensity of serum SCL was observed: 4.0 ± 0.9, 1.7 ± 0.2, and 0.7 ± 0.2 sec^{-1}, respectively, compared with 10.3 ± 0.5 sec^{-1} in the control. A decrease in the intensity of SCL also was observed 1, 2, and 3 months after the 3rd injection (at intervals of 7 days) of DMBA intravenously into the rats: 14.4 ± 2.6, 9.2 ± 1.6, and 1.9 ± 1.2 sec^{-1}, respectively (24.4 ± 1.7 and 22.7 ± 1.6 sec^{-1} at the beginning and end of the experiment). After a single injection of DENA (100 mg/kg), on the other hand, an increase in SCL was observed: 3, 6, 10, and 13 months after injection the intensity of SCL was 31.0 ± 3.8, 36.2 ± 4.1, 42.7 ± 6.6, and 92.2 ± 14.0 sec^{-1}, respectively. In the control, on the other hand, this parameter fell with age from 30.2 ± 4.7 to 16.4 ± 1.4 sec^{-1}.

Thus the presence of significant differences in the direction of changes in the blood serum SCL level during growth of different kinds of tumors was demonstrated on 10 experimental models of carcinogenesis and tumor growth: five strains of transplantable tumors, two strains induced by oncogenic viruses, and three induced by chemical carcinogens. It can be tentatively suggested that these differences in the kinetics of SCL reflect differences in the relations of rats of synthesis and "pumping over" of antioxidants into the growing tumor in different tumor processes, and also differences in the endocrine regulation of metabolic processes [14], which are a matter for special study. Consequently, the decrease in the intensity of blood serum (plasma) chemiluminescence, described by Zhuravlev [6] for Walker's carcinosarcoma and by Tarusov [13] for certain other transplantable tumors, is not a general rule.

We obtained similar data in clinical oncology during treatment of more than 1000 patients. In tumors of the esophagus, stomach, and cervix uteri and epidermoid tumors of the lungs, a typical finding was an increase in the intensity of SCL, parallel with the extent of spread and the severity of the tumor. In adenocarcinomas of the lungs, this parameter decreased by 30-50%, a matter of differential diagnostic importance [14].

The important discovery is that notwithstanding all the different trends observed on different models, changes in the intensity of serum SCL correlate closely with the kinetics of tumor growth. In every case for which we have adequate information, the extremal points on the curve of intensity of SCL coincided with times of change in the kinetics of tumor growth.

What lies at the basis of this general pattern? It will be recalled that the intensity of SCL is an integral characteristic of the relationship between pro- and antioxidant stimuli at the time of investigation: the quantity and degree of unsaturation of fatty acids of the serum lipoproteins; the quantity and activity of fat- and water-soluble antioxidants; activity of enzyme systems, both oxidative and antioxidative; the number of ions of metal catalysts of FRO [10, 11]; and finally, hormones – thyroid, steroid, and catecholamines [14]. During tumor growth all these factors change in various directions. In particular, the number of metal ions falls in the blood and organs of animals with tumors of different nature [5]. To elucidate the mechanisms of carcinogenesis and anticarcinogenesis, we must study and compare all these changes. However, integral information provided by a nondestructive method such as SCL is interesting on its own account, for it characterizes relations between these factors in the course of time [14].

It can be tentatively suggested on the basis of these data that either a relationship of cause and effect exists between pro-antioxidative equilibrium, on the one hand, and the intensity of tumor growth on the other hand, or both these parameters are consequences of a certain fundamental mechanism of carcinogenesis. The random character of correlation between the kinetics of SCL and the kinetics of tumor growth seems to be unlikely .

LITERATURE CITED

1. V. A. Baraboi, V. L. Ganul, A. V. Evtushenko, et al., Vopr. Onkol., No. 1, 51 (1980).
2. V. A. Baraboi and V. É. Orel, Biochemiluminescence [in Russian], Moscow (1983), pp. 222-240.
3. V. A. Baraboi and V. É. Orel, Fourth National Congress on Oncology: Abstracts [in Bulgarian], Vol. 4, Sofia (1985), p. 19.
4. E. B. Burlakova, A. V. Alesenko, E. M. Molochkina, et al., Bioantioxidants in Radiation Damage and Malignant Growth [in Russian], Moscow (1975).
5. Ya. I. Gonskii, G. A. Babenko, V. V. Vagilevich, et al., Problems of Interaction between Organism and Tumor [in Russian], Kiev (1982), pp. 98-100.
6. A. I. Zhuravlev and A. I. Zhuravleva, Very Weak Luminescence of Blood Serum and Its Role in Diagnostic Strategy [in Russian], Moscow (1975).
7. I. I. Ivanov and B. N. Tarusov, Physicochemical Mechanisms of Malignant Growth [in Russian], Moscow (1970), pp. 112-115.
8. Yu. A. Umanskii (ed.), Immunology of Viral Carcinogenesis [in Russian], Kiev (1978).
9. R. E. Kavetskii, Interaction between Organism and Tumor [in Russian], Kiev (1977).
10. A. V. Keis, V. A. Polevskii, V. E. Formazyuk, et al., Byull. Éksp. Biol. Med., No. 8, 45 (1983).
11. Yu. M. Lopukhin, Yu. A. Vladimirov, M. N. Molodenkov, et al., Vopr. Med. Khimii, No. 1, 116 (1983).
12. V. G. Pinchuk, V. A. Baraboi, Ya. I. Serkiz, et al., Vest. Akad. Nauk Ukr. SSR, No. 1, 57 (1986).
13. B. N. Tarusov, Biophysics of Cancer [in Russian], Kiev (1976), pp. 107-126.
14. V. A. Baraboi and E. E. Chebotarev (ed.), Chemiluminescence of Blood in Experimental and Clinical Oncology [in Russian], Kiev (1984).
15. N. M. Émanuél', Kinetics of Experimental Tumor Processes [in Russian], Moscow (1977).