(see Figure 1). Further reduction on temperature of saline solution to 5°C caused an even greater decrease on the rate of healing; about 15% of the initial injury potential remained for 30 min after lesion (see Figure 1). From the curves presented in Figure 1, the time constant of the rate of healing was determined for each group of experiments. As shown in Figure 2, such time constant proved to be a linear function of the inverse of temperatur. The temperature coefficient (Q_{10}) of the rate of healing, measured in this way, between 25° and 15°C is 4.7 indicating a high activation energy for this process.

Measurements of resting potential of non-damaged cells performed with intracellular microelectrodes also indicated that at low temperature the depolarization produced by lesion is not totally reversed in the non-injured cells located 500 μm or more from the lesion. On the other hand, it was found that the resting potential of toad's ventricular fibers at 25°C was 80 mV (S.E. ±1.5) at 15°C–78 mV (S.E. ±1.2) and at 5°C –76 mV (S.E. ±1.8). Similar results have previously been reported in frog ventricular muscle[6] in which changes on temperature from 0.3 to 24°C caused neglegible variation in resting potential. The fact that injury potentials can easily be elicited at low temperatures is another indication that membrane polarization is not drastically altered. In salivary glands the failure of the sealing process found at low temperature seems to be related to cell uncoupling[7]. The influence of temperature on the electrical coupling between heart cells was investigated by impaling 2 microelectrodes close together (50 to 70 μm); hyperpolarizing pulses of current were injected through 1 electrode and the voltage changes were recorded with the other electrode. The results obtained indicated that the electrical interaction between myocardial cells of toad is slightly altered by reducing the temperature (see Figure 3).

The present results indicate that the healing-over process in toad's myocardium is largely dependent upon temperature and that the depression on the rate of healing is not due to cell uncoupling as in epithelia[8,9].

Résumé. L'influence de la température dans le phénomène de suppression des potentiels de lésion «healing-over» du muscle cardiaque de *Bufo marinus* est édudiée avec des électrodes extracellulaires. A la température de 15°C ou 5°C, une réduction marquée de la vélocité de suppression est observée.

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Release of Fibrinolytic Activators from Human Tumours Cultured in vitro[1]

Tumours possess coagulative properties[2,3] and the ability to develop fibrinolytic activity[4–7]. Fibrin degradation procucts (FDP) have been demonstrated in the serum and in very high concentration in ascitic fluid from patients with malignant ovarian tumours[8]. These findings are presumably connected with the fibrinolytic activity of the neoplasms.

This paper reports the release of fibrinolytic activators from human oral tumours cultured in vitro (Table I). The tumours were excised under local anaesthesia (Lidocain® 2% with Exadrin® 12.5 μg/ml) and divided under sterile conditions. One part was set aside for histopathological examination, while the other was studied for its capacity to release fibrinolytic agents in organ culture with the method described previously[9]. Explants from the tumours were cultured as organ cultures on gelatine foam (Spongostan®) in Leighton tubes containing 1 ml Parker 199 (SLB, Stockholm) synthetic medium and a preformed clot obtained by adding 1 ml human fibrinogen (Kabi Stockholm 1% in distilled water) to 0.02 ml of thrombin (Topostasin® 75 NIH U/ml saline). Penicillin and streptomycin was added to the Parker solution in order to prevent infection.

Each tube contained 6 tumour explants distributed on 2 slices of gelatine foam. Every 24th h after the beginning of the culture, a small volume (0.06 ml) of medium was aspirated and assayed quantitatively for fibrin degradation products (FDP) according to an immunological method[10].

At the end of the culture period (3 days), the explants were examined histochemically for activation of fibrinolysis by a modified fibrin slide technique[11]. Some explants were fixed in Bouin's solution and examined by routine histology.

In all tumours examined, FDP appeared in progressively increasing amounts. A culture experiment is shown in Table II. The mean values of FDP found in the culture medium are given in Table I. There was a considerable difference in the fibrinolytic activity of different tumours. The highest activity was found for epulis angiomatosa. Addition of Tranexamic acid (AMCA) in the culture medium completely inhibited fibrinolysis suggesting that the agent liberated is an activator of plasminogen since AMCA mainly affects fibrinolysis by exerting a competi-

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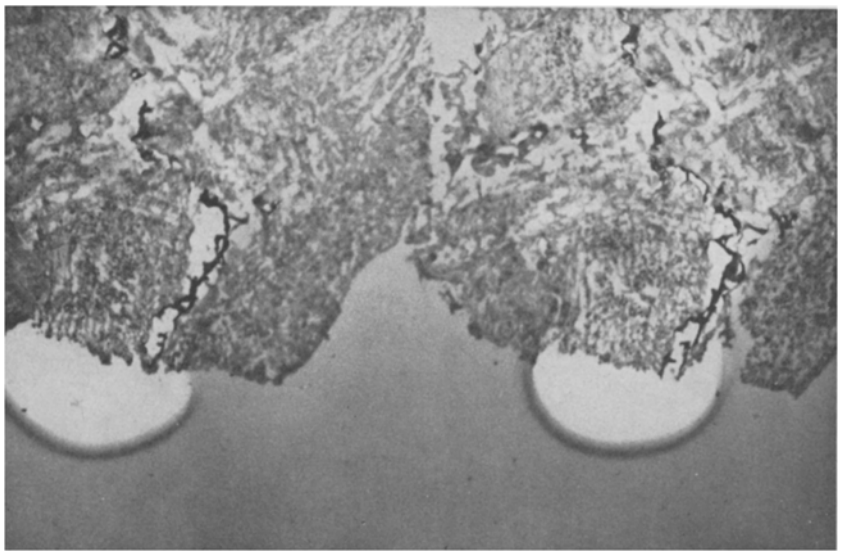

Explants of cancer palati duri after 3 days of culture examined by the fibrin slide technique. Fibrinolysis (pale areas) is present in the sections. ×15.

Table I. Mean values of FDP in the culture medium (mg/100 ml) of different tumours

Tumour	Day I	II	III
Fibroma	0	8.0	—
Granuloma teleangiectaticum	1.3	8.3	—
Cancer	0	2.5	63.5
Adenoma pleomorphum	0	0	5.5
Epulis angiomatosa	6.5	30.0	95.0
Epulis gigantocellularis	1.4	13.0	76.0
Haemangioma	2.2	10.0	43.0

Table II. FDP in the culture medium (mg/100 ml) of cultures of an epulis angiomatosa

Culture	Day I	II	III
1	0.7	6.8	80
2	1.0	8.0	59
3	1.0	11.0	108
4	1.0	2.9	40
5	1.0	5.4	56
6	3.5	4.6	116
Control 1	0	0	traces
Control 2	0	0	0

tive inhibition on plasminogen activators and has no inhibitory effect on proteases such as plasmin and trypsin at the concentration used (1 mg/ml)[12]. Routine histology revealed good survival of the explants, suggesting that AMCA had no toxic effect on tissue growth. FDP never appeared in the medium of controls, consisting of gelatine foam without explants. Histological examination of the explants after culture revealed persisting fibrinolytic activity (Figure) in all the specimens examined.

Vascularization and growth of tumours requires a fibrin network as a matrix[3] and fibrinolytic activity is probably necessary for the successive breakdown of this matrix. The very high concentrations of FDP in malignant ascitic fluid[8] suggests a high fibrinolytic activity of the malignant tumour cells. In this investigation, only one of the tumours was malignant and no difference was seen between this tumour and the benign tumours.

There is evidence that the fibrinolytic activity of different tissues often varies with their vascularity[13]. In the present series, the release of fibrinolytic substances was greatest in a highly vascularized angioma. It is possible that the fibrinolytic activity developed by a tumour varies with its vascularity more closely than with its degree of malignancy. Our results also suggest that tumours may release fibrinolytic agents into the circulation and enhance systemic fibrinolysis.

Zusammenfassung. Unter Verwendung einer Methode, welche die Bestimmung der fibrinolytischen Aktivität in Organkulturen erlaubt, wurden verschiedene orale Tumoren untersucht und dabei eine Korrelation zwischen der Vaskularisierung der Tumoren und der entwickelten fibrinolytischen Aktivität festgestellt. Dagegen konnte kein Unterschied in der fibrinolytischen Aktivität von malignen und benignen Tumoren nachgewiesen werden.

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