Après 20 min, le mouvement cytoplasmique de la cellule protégée est activé. Sa vitesse devient supérieure à celle qui l'animait avant l'irradiation de sa cellule voisine. Ce phénomène perdure 3 h environ.

Certaines cellules cependant manifestent à nouveau une courte accélération de leur flux protoplasmique après un temps de latence de 5 h. Pendant toute la durée de l'expérience, la vitesse de la cyclose chez la cellule protégée reste supérieure à celle de la cellule témoin. Cette différence de vitesse est statistiquement significative.

Dans la cellule traitée, la reprise de la cyclose a lieu 10 min après la fin de l'irradiation. Cette cellule ne retrouve cependant pas sa pleine vitalité puisque la circulation protoplasmique n'atteint plus au maximum que 65% de sa valeur initiale. Notons que cette valeur est supérieure à celle observée dans le cas d'une cellule isolée et irradiée à cette dose (55%: GILLET[4]).

Discussion. L'accélération du flux protoplasmique dans la cellule voisine de celle qui a été irradiée peut s'expliquer par le passage de certains métabolites de l'une à l'autre. Une action induite par la conduction d'un influx de nature électrophysiologique est en effet exclue après un temps de latence aussi long que 20 min.

FRIDVALSKY[5] a observé que les membranes transversales des cellules internodales et nodales des Charophyceae sont percées de pores nombreux de 400 mμ de diamètre, permettant ainsi un échange métabolique aisé entre les différentes cellules. Le cytoplasme de la cellule irradiée est donc facilement en relation avec celui de la cellule protégée.

La nature de l'information chimique induite par l'irradiation et transmise à une cellule voisine reste cependant à préciser. S'agit-il de substances énergétiques libérées ou emmagasinées dans la cellule irradiée incapable de les utiliser, ou plutôt de métabolites toxiques diminuant la viscosité du cytoplasme de la cellule adjacente? Ces hypothèses sont à l'étude actuellement.

La faible diminution observée dans l'activité du protoplasme de la cellule-témoin après les premières minutes est sans doute due à la manipulation elle-même (exposition pendant 5 min à l'air sous le générateur de rayons X ne fonctionnant pas). Cette diminution est un peu plus forte que celle observée dans un travail précédent. Elle n'est pas surprenante car quelques auteurs ont déjà insisté sur le comportement différent des cellules internodales de *Nitella* pendant les mois d'hiver (KAMIYA[6]).

Conclusions. (1) L'irradiation d'une cellule internodale de *Nitella flexilis* détermine dans la cellule internodale voisine une accélération transitoire du courant cytoplasmique. De plus, pendant 8 h au moins, la vitesse de ce dernier demeure supérieure à celle observée chez les cellules internodales témoins. (2) Il est probable que ce phénomène ait lieu par la médiation de facteurs chimiques induits dans la cellule irradiée.

Summary. Irradiation of an internodal cell of *Nitella flexilis* induces in the adjacent internodal cell a transitory acceleration of cytoplasmic streaming; during 8 h at least the speed of this streaming is higher than in control internodal cells. It is probable that this phenomenon is due to transfer of certain substances from the irradiated cell.

C. GILLET

Institut de Morphologie Végétale et Laboratoire de recherches pour la protection des populations civiles, Liège (Belgique), le 17 janvier 1963.

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Hormonal Influence on Metastatic Spread of the Yoshida Sarcoma

BALLINI et al.[1] have recently reported that the transplantation of organs from Yoshida-bearing rats is able to produce tumor growth into recipient animals. The repeated observation by many of the absence of visceral metastasis in Yoshida-bearing animals, together with the findings mentioned above, indicates that metastasis formation is determined by multiple factors, perhaps related to the host, besides tumor cell viability and invasiveness.

The influence of cortisone on metastasis production was first demonstrated by AGOSIN et al.[2] in 1952. Since then several investigators, dealing with a varied spectrum of experimental tumors, have variously reported an increase, decrease or no alteration in the incidence of metastasis in cortisone treated animals[3-5]. BEUTHNER et al.[6] reported that the metastatic localization of intravenously injected Yoshida sarcoma cells can be modified by treatment with ovarian hormones. In treated rats, the metastases were mainly in mammary glands, ovaries and uterus, whereas in untreated animals, the adrenals, intestines, lungs and the mesenteric and paravertebral lymph nodes were the sites affected.

That the site of tumor implantation can also influence the metastatic spread was shown by BASERGA et al.[7]. Working with a tumor that produced no metastasis when implanted into the subcutaneous tissue of the trunk, they obtained pulmonary secondaries by injecting tumor cell suspension into the subcutaneous tissue of the tails of mice.

In this paper we report the findings regarding the action of testosterone, estrogen and cortisone on the behaviour of the Yoshida sarcoma, implanted in the tails of Wistar rats.

Wistar female rats, weighing about 150 g were used. 10 ml of Yoshida ascites fluid was centrifuged, the supernatant discarded and the sediment suspended in 10 ml of sterile saline. Approximately 0.2 ml of this suspension was injected into the subcutaneous tissue of the middle of the tail in 39 rats. Care was taken to avoid the lateral vein, and the resistance set up by the plunger of the syringe

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during the injection made sure that in every case we reached the subcutaneous tissue only.

The animals were divided into four groups and treated as follows:

Group 1 (9 rats) received daily injections of 10 mg of testosterone intramuscularly, starting 24 h after tumor transplantation. – Group 2 (9 rats) received daily injections of 5 mg of estrogen intramuscularly, starting 24 h after tumor transplantation. – Group 3 (9 rats) received daily injections of 5 mg of hydrocortisone acetate intramuscularly, starting 24 h after tumor transplantation. – Group 4 (12 rats) the animals in this group were implanted, with the tumor and left untreated as controls.

The commercial hormonal preparations used were: Testoviron, Schering; Stilbestrol, Johonson and Johnson, and Solu-Cortef, Upjohn. The animals were sacrificed 15 days after the beginning of the treatment and autopsies performed.

A local growth in the tail was detected in 30 animals. The tumors grew lengthwise along the tail, more frequently from the middle towards the root, giving to this appendix a sausage-like appearance. All the 12 controls rats exhibited a local growth which varied conspicuously in size from rat to rat. No visceral metastasis could be discovered in them.

In the hormone-treated animals, the preferential sites for metastasis were the mediastinal lymph nodes, kidneys, lungs, heart and paravertebral lymph nodes. The liver, spleen, mammary glands, uterus, ovaries, intestines, adrenals and brain were free of metastasis. In the Table is registered the incidence of grossly visible metastasis

	Rat	Local growth (tail)	Metastasis Lung	Heart	Kidney	Lymph node
Cortisone	1	+	+	+	+	+
	2	+	+	—	—	+
	3	+	—	—	—	+
	4	+	—	—	—	—
	5	+	—	—	—	—
	6	+	—	—	—	—
	7	+	—	—	—	—
	8	+	—	—	—	—
	9	—	—	—	—	—
Total positive		8	2	1	1	3
Estrogen	1	—	+	—	+	+
	2	—	—	—	+	+
	3	—	—	—	+	+
	4	—	—	—	—	+
	5	+	—	—	—	+
	6	+	—	—	—	—
	7	+	—	—	—	—
	8	+	—	—	—	—
	9	+	—	—	—	—
Total positive		5	1	0	3	5
Testosterone	1	+	+	+	+	+
	2	+	—	—	+	+
	3	+	—	—	+	+
	4	+	—	—	—	+
	5	+	—	—	—	+
	6	—	—	—	—	+
	7	—	—	—	—	+
	8	—	—	—	—	—
	9	—	—	—	—	—
Total positive		5	1	1	3	7
Controls		All 12 controls exhibit local growth and did not show visceral metastasis				

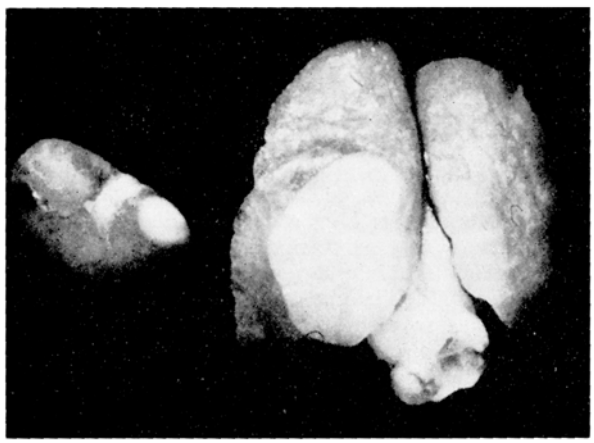

Fig. 1. Estrogen-treated animal. Metastasis in mediastinal lymph node, lung and kidney.

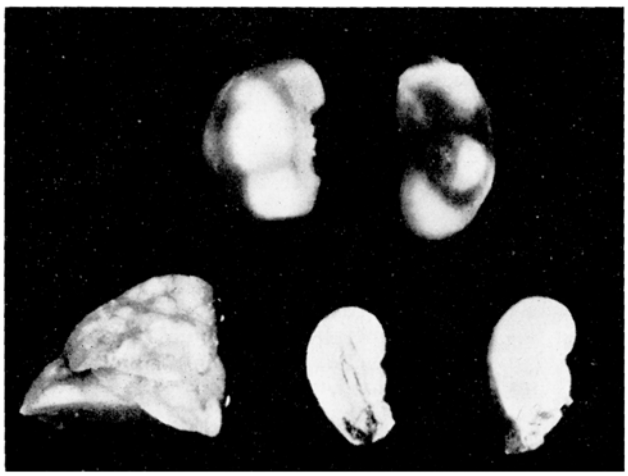

Fig. 2. Cortisone-treated animal. Metastasis in lung, heart and kidneys. The heart is entirely invaded by the growth.

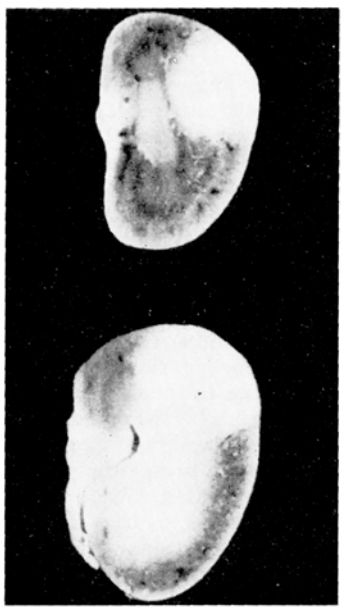

Fig. 3. Testosterone-treated animal. Metastasis in both kidneys.

only. We should mention that on microscopic examination two more animals in the testosterone-treated group and one more in the cortisone-treated group showed pulmonary micro-metastasis, which, had the animals been allowed to survive longer, would have grown to grossly visible size.

It is worth noticing that the local growth of the tumor was not a necessary condition for the appearance of the metastasis. This apparently paradoxical effect, first pointed out by AGOSIN et al.[2], was particularly evident in our estrogen-treated rats. Among them, the three animals with kidney metastasis did not show any sign of tumor growth in the tail and if we take the three groups together a significant incidence of mediastinal metastasis could be demonstrated in the absence of primitive growth. The microscopic picture of the metastatic growth did not show any peculiarity. In the lungs the tumor nodules were frequently centred by a vessel where a tumor emboli could occasionally be depicted. The growth in the kidneys and heart led to destruction of the organ structures and also infiltrates interstitially to a great extent.

The total absence of metastatic growth in all the twelve controls, despite the local growth, seems to exclude the view that the modification of the behaviour of this tumor was attained by its growing in the tail. Besides, the appearance of metastasis in treated animals which did not show local growth indicates that it is not only the easiness to penetrate voluminous vessels, in this case the lateral vein of the tail, which explains the modified behaviour[7]. Rather it seems that the hormonal treatment created certain conditions in the host that facilitated the arrest and proliferation of circulating tumor cells in sites which are usually unaffected in non-treated rats. The incidence of extra-pulmonary metastasis was highly significant in our material, showing that the pulmonary microcirculation is promptly traversed by the Yoshida neoplastic cells.

Direct experimental observation *in vivo* has shown that cortisone increases endothelial sticking of blood-borne tumor cells[8]. Cortisone also alters the lipid metabolism and increases blood coagulability[9]. As a matter of fact, the majority of the experimental factors that increase hematogenic metastasis produce a potential hypercoagulability and/or increases leucocytic sticking as pointed out by WOOD et al. and several others investigators[3,10–15].

The state of the endothelial surface and blood coagulability seem then to play a decisive role in the determinism of metastatic localization and growth of blood-borne neoplastic cells and are probably the preeminent host factors involved in the mechanism of metastasis formation[3,16]. We have so far no explanation regarding mechanism of action for the production of metastasis by treatment with sex hormones. However, it is not out of question to postulate that these hormones exert their action through some modifying effect on endothelial adherence and blood coagulability, as demonstrated for cortisone.

If this observation with the Yoshida sarcoma proves to be a general fact, a warning should be sounded concerning the utilization of sex hormones in clinical management of cancer patients, owing to a possible acceleration of metastatic dissemination in hormone-treated individuals, as has already been indicated in some recent papers[17–20].

Zusammenfassung. Es wird über die Verbreitung des metastatischen Yoshida-Sarkoms bei Ratten berichtet, die das Sarkom in den Schwanz geimpft erhielten. Die geimpften Tiere wurden mit Testosteron, Cortison und Östrogen behandelt. Die einfache Einpflanzung des Sarkoms ist nicht genügend, um die Verbreitung der Geschwulst zu veranlassen.

J. P. GUIMARÃES, I. BALLINI, and M. C. SANTOS MOTTA

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Analysis of the Radioisotope Renogram[1]

The estimation of organ function, by external counting of γ-emissions from an administered radioactive substance, has been widely employed in thyroid studies. Since the kidneys accumulate and excrete certain radiolabeled dyes, the same type of approach is possible. The procedure which was evolved by WINTER[2] was termed the radioisotope renogram. Attempts at quantitation have been empirical thus far[3,4]. We wish to point out possible quantitation of the radioisotope renogram, based on a simple 4 compartment system.

Shown in the Figure is a possible model of the events following intravenous injection of a small quantity of a radioactive substance which is excreted by the kidneys (for example, the commonly employed 0.2 mg of *o*-iodohippuric acid represents only 7×10^{-7} moles; if distributed evenly in 5 l of blood, the concentration would be 1.4×10^{-7} *M*). At low concentrations there need be little concern with saturation of the renal excretory mechanism. Passage of the substance from blood to kidney and from kidney to urine, even if 'active transport', can be considered as a linear function of concentration at such great dilutions. It is also apparent that the reverse reactions (passage of material from kidney to blood, and from urine

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