specific areas of inflammation in the lungs which were characterized by the presence of nodular mononuclear cell infiltrates. Secondary to the lungs, other inflammatory observations were vacular (lipidic) changes associated with small areas of necrosis and inflammation, and small aggregates of polymorphonuclear leucocytes in the liver. Finally, the bone marrow was acellular and, occasionally, hyperplastic lymph nodes were noted.

In the present study, the use of Ara-C produced a varied response regarding the 3 aspects of the autoimmune response, namely, 1. humoral anti-body production; 2. delayed hypersensitivity; and 3. immunopathological lesions. The drug appeared to cause a slight depression in the humoral antibody response to homologous thyroid antigen by day 36 postimmunization. The skin test response indicated a more intense delayed hypersenstive response in the drugtreated, immunized animals than in comparable controls. Also, more of the guinea-pigs treated with Ara-C responded to skin testing. In this regard, one cannot rule out the possibility that non-immune, inflammatory changes had influenced the skin response. Immunopathological lesions, the third facet of the autoimmune response, was less influenced by the presence of Ara-C; nevertheless, fewer severe lesions were observed in the drug-treated animals. In summary, Ara-C produced only a mild suppressive effect on thyroid autoimmune induction and was unsuccessful in preventing tissue damage.

The cellular immune aspects of the autoimmune response appeared independent of the humoral response for the production of thyroid lesions. Once the cellular response had been initiated for action, it was not susceptible to the continuous insult and exposure to the body caused by the presence of Ara-C. The antigen sensitive dividing cell populations were either sheltered from Ara-C exposure or had undergo sufficient cell division before the drug could be effective. Thyroglobulin or thyroid antigen is thought to require processing by thymic derived cells or macrophages before presentation to the antibody-receptors of sentivive cells[12]. This step may not have been affected by the drug since the cellular immune responses were not greatly influenced and thyroid histologic lesions were evident. In addition, histological changes were not prevalent in either the thymus, spleen, or lymph nodes. Thus, the adminsitration of cytarabine via the i.p. route during immunization does not appear to inhibit the cellular immune response in thyroiditis.

Zusammenfassung. An einer Untersuchungsserie experimentell induzierter Autoimmunthyreoiditis beim Meerschweinchen wird gezeigt, dass Cytosine Atabinoside nur einen geringen suppressiven Effekt auf die Autoimmuninduktion hat und die Gewebezerstörung nicht zu verhindern vermag.

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The Effect of Prostaglandin on Tumour Implantation

The prostaglandins (PGs) are ubiquitous tissue hormones with a wide variety of biological activities[1]. They mediate i.a. the inflammatory and allergic response[2,3] by promoting the diapedesis[4] and migration[5] of leucocytes.

The rejection of a non-malignant homograft is the result of a local delayed hypersensitivity reaction mounted by the recipient[6]. Malignant homografts fail to elicit this response[7]. It is believed that tumour secretes a PG antagonist and that the PG deficiency so induced is the cause of the immunological paralysis in the vicinity of tumour[7,8].

On this hypothesis, the addition of large amounts of PG to the tumour inoculum would counterbalance the PG deficiency, re-instate the delayed hypersensitivity response and so lead to the rejection of the graft. The present communication reports on some relevant experiments.

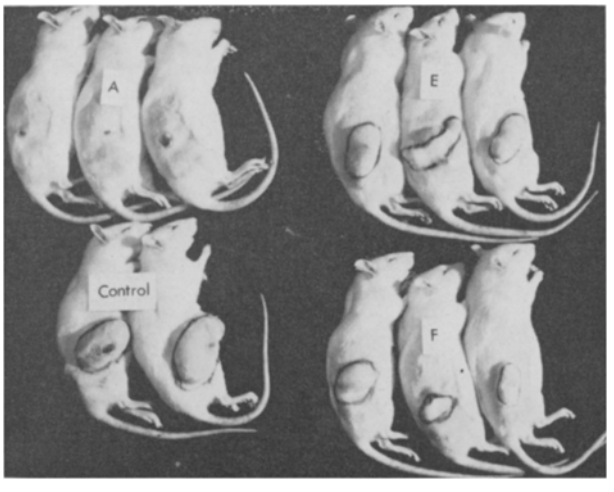

Fig. 1. Tumour growth in 4 groups of rats 3 weeks after inoculation of tumour suspended in solutions of PG A, E and F or solvent. The recipients of PGA have small ulcers but no tumour.

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Tumour growth in rats inoculated with tumour suspended in solutions of 1 mg/ml PG A2, E2 and F2 or solvent

Site of inoculation	PGA2	PGE2	PGF2	Solvent
Subcutaneous weanling	16/31	6/6	6/8	27/27
Intramuscular weanling	16/16	1/1	2/2	15/15
Subcutaneous neonate	4/4	4/4	—	10/10

Materials and methods. Animals. White Wistar rats, weanlings weighing 80–100 g and pregnant females were obtained from Messrs. Tuck and Son, Rayleigh. Tumours. A chemically induced tumour[9] was maintained by serial passage and used in these experiments. Chemicals. PGs A2, E2 and F2 were obtained by courtesy of the Upjohn Co. Kalamazoo, Mich. and prepared as a solution of 1.0 mg/ml by the method indicated by the manufacturers.

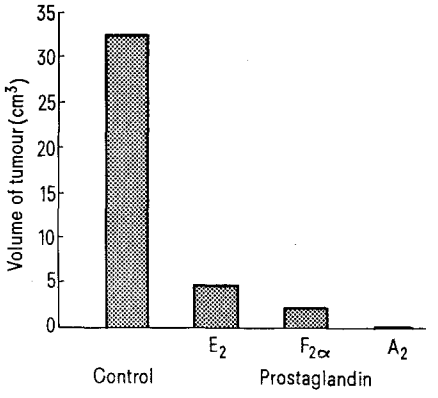

Fig. 2. Mean tumour volumes in 4 groups of weanling rats bearing subcutaneous tumour.

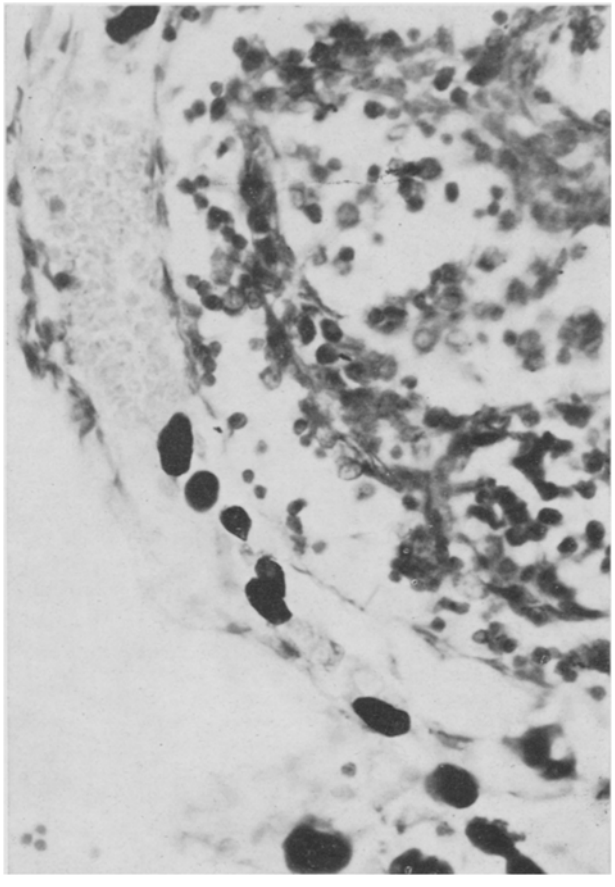

Fig. 3. Injection site 6 days after subcutaneous inoculation of 0.3 ml of tumour suspended in PGA solution. Extravasation of immunoblasts to invade the graft site. The blast cells are black in this photograph. Methyl green pyronin. ×420.

Preparation and administration of tumour suspensions. 1 volume of tumour was suspended in 2 volumes of saline, homogenized in a MSE homogenizer at 10.000 rpm for 90 sec. For the PG assays the tumour suspensions were centrifuged, the supernatant discarded and the sediment resuspended in PG solutions or solvent to make up the original volume. Amounts of 0.3 ml were injected s.c. or i.m. into weanling rats. Neonatal rats received doses of 0.05 ml into the nuchal region.

Histological methods. Injection sites were excised on the 6th post-implantation day, fixed in formol saline and stained with haematoxylin eosin or methyl green pyronin.

Results. Tumours suspended in solutions of PG A2 and injected s.c. into weanling rats failed to take in about 50% of the test animals (Table and Figure 1), and the tumours that did take were considerably smaller than those of the other experimental or of the control animals (Figure 2). Concentrations of PG lower than 1.0 mg/ml were ineffective.

Histological examination of the graft site of tumours suspended in solvent showed, by day 6, a focus of proliferating tumour cells which also spread to the underlying connective tissue. Some very few lymphocytes and immunoblasts were seen at the periphery of the graft.

The injection site of tumour suspended in PG presented a very different picture. There were large numbers of immunoblasts traversing the capillary walls to migrate towards the graft site. Only very few morphologically intact tumour cells were seen (Figure 3).

Tumour suspended in PG solution grew well at sites of immunological privilege i.e. in striated muscle and in neonatal subcutaneous tissue (Figure 4). Histological examination of these areas confirmed the absence of a white cell reaction in and around tumour. The PG injections were well tolerated. Attempts at intracerebral inoculation led to the instant death of the animal.

Discussion. Apart from the promotion of the diapedesis and migration of leucocytes, the PGs have also been shown to inhibit the growth of malignant cells[10] and to enhance the differentiation of tumour cells in culture[11]. These mechanisms do not seem to be responsible for the inhibition of subcutaneous tumour in our experiments. If the PGs were directly cytopathic to tumour cells, tumour cells exposed to PG would fail to grow at all sites. Yet, tumours suspended in solutions of PG A, E and F took and grew at sites of immunological privilege such as in striated muscle of weanlings and in subcutaneous tissue of neonates[12,13] though in the latter case only very small doses were used. Moreover, tumour suppression only occurred in association with an intense delayed hypersensitivity reaction mounted by the recipient.

PG A is more stable than other PGs[14] and this may account for the more favourable results obtained with this substance.

The PGs – in order to be effective – had to be administered in high doses, far above the normal, physiological concentrations. However, it must be remembered that the homograft response is a biphasic reaction. There are 2 consecutive waves of mononuclear cells invading the graft site, the first soon after implantation, the second

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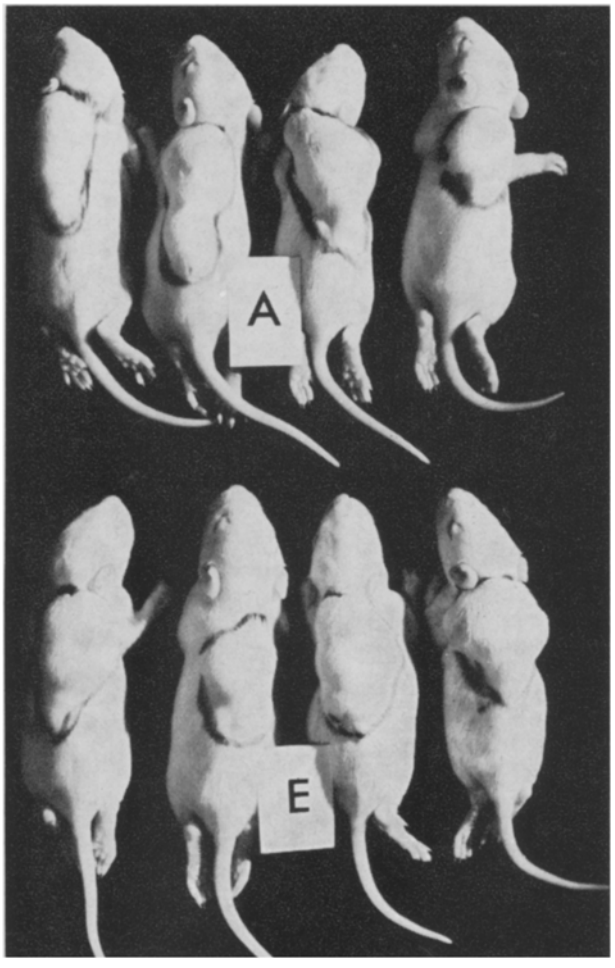

Fig. 4. Two groups of rats inoculated with tumour suspended in PGA and PGE solutions within 24 h of birth. Normal tumour growth 3 weeks after inoculation. No difference in size between the PGA and the PGE group.

beginning on the 6th day[6,8]. The second phase is the effector phase[8]. Sufficient PG must be available at the graft site to promote the diapedesis and migration of monocytes in both phases and at the same time, to counterbalance the PG antagonist secreted by tumour.

The above considerations obviously also hold true for the injection of PG into established i.e. 6-day or older tumour. Administration of PG would induce the initial phase on the 6th-7th day and the second effector phase on the 13th–14th day. By that time the tumour would have attained a diameter of at least 20 mm. The amounts of PG required to induce an effective mononuclear infiltration into tumour of that size, would have to be very large. Large amounts are likely to be poorly tolerated[15].

From these observations it appears that the PGs, particularly PG A2, are capable of inhibiting the implantation of tumour cells. They are not indicated as a treatment of established tumour.

Zusammenfassung. Allergische Reaktionen werden unter anderem durch Prostaglandin erzeugt. Krebsgewebe produzieren eine prostaglandinhemmende Substanz, und es wird nachgewiesen, dass grosse Dosen von Prostaglandin diese Substanz neutralisieren und eine allergische Reaktion um die Krebszellen hervorrufen, wodurch die Implantation der Tumorzellen verhindert wird.

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Niflumic Acid, Prototype of a Multiaction Antithrombotic Agent[1]

Antiaggregating agents, anticoagulants, and fibrinolytic enzymes each possess only one single antithrombotic property, thus interfering with just one phase of the intravascular clotting process. In this communication the interesting combination in principle of antithrombotic properties, of the antirheumatic drug, Niflumic acid (3-fluoromethyl-3-phenylamino-2-nicotinic acid)[2] is reported.

Methods. Enhancement of fibrinolytic activity induced by streptokinase and urokinase by Niflumic acid (Siegfried, Zofingen/Switzerland) was measured with the rotating standard clot[3]. This cylinder-shaped clot can be lysed on one end only, thus imitating a small human vessel which is completely occluded by a thrombus. The rate of its dissolution is read in microliters. The fibrinolytic activity exerted by Niflumic acid was assessed by determining the lowest molarity inducing fibrinolytic dissolution of a human hanging plasma clot[4] after 24 h incubation. Clots were suspended either in buffered saline pH 7.4 (BS) or human plasma which was heparinized (1 unit/ml) in order to prevent clotting caused by the thrombin released from the dissolving clot. Only plasma which dissolved within 12 h when clotted in presence of 7.5 units streptokinase was used. With the use of N_2H_4, the hanging clots were preincubated in BS containing 2.5 m*M* N_2H_4 for 3 h before Niflumic acid was added, and the mixture was then incubated for 24 h. The fibrin plates were made from a 2.5% solution of commercial human fibrinogen in BS. The fibrinolytic activity induced in rats by Niflumic acid was assessed with the micro-euglobulin lysis time[5], its effect on collagen-induced aggregation of platelets in plasma with the Dual Sample Aggregometer[6], and its inhibition of fibrinogen-

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