must indicate either that the cells produce too little chalone or that, as with the V × 2 epidermal tumour and the chloroleukaemia (see preceding communications), the chalone that is produced is rapidly lost into the blood.

It is now known that at least four different transplantable tumours continue to synthesize the chalones of their tissues of origin and also to respond to their own chalones by mitotic inhibition when the concentration is increased sufficiently. In melanomata it is even possible to suppress the mitotic activity by extracts of melanomata. Again it is possible that tumour growth *in vivo* may be prevented or even reversed by repeated injections of either normal or tumour tissue extracts. A preliminary examination of this possibility is described in the following communication.

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Melanoma Regression induced by "Chalone": a New Tumour Inhibiting Principle acting *in vivo*

TISSUE-SPECIFIC anti-mitotic substances, now known as chalones[1], have been extracted from a number of tissues, and especially well known are the epidermal and granulocytic chalones[2,3]. Although it is tissue-specific the epidermal chalone is not species-specific[4]. The various chalones evidently play an important part in the regulation of tissue growth, and so it is necessary to consider whether in a tumour the chalone system may have become deranged. Recent studies of several different tumours have shown that chalones are present and that the tumour cells are still able to respond to them by mitotic inhibition (see preceding communications). In all cases the high mitotic activity of the tumour appears to be related to the low chalone concentration within the cells. This suggests the possibility of suppressing neoplastic growth by repeated chalone injections, and a preliminary investigation has now been carried out.

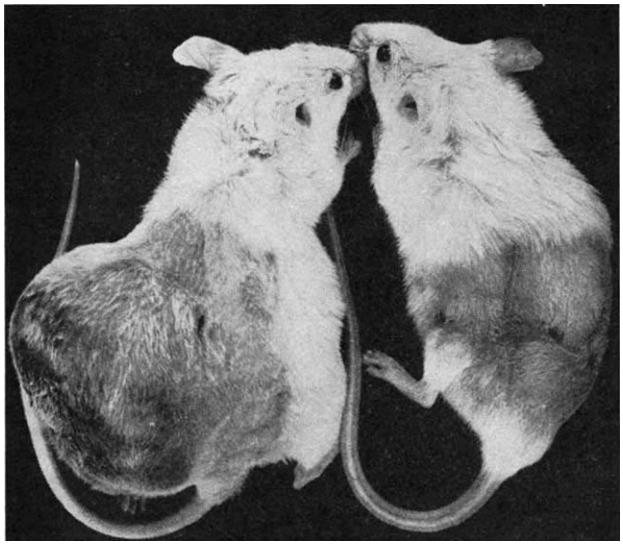

Fig. 1. NMRI mice with Harding–Passey melanoma: left, an untreated control and, right, a similar mouse after treatment with pig skin extract. In the treated mouse note the healing wound after the extensive ulceration which accompanied tumour regression.

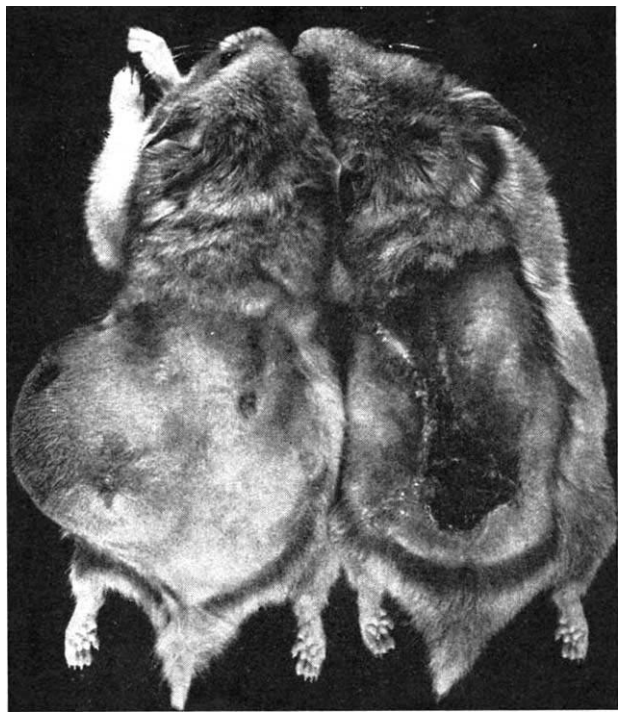

Fig. 2. Syrian hamsters with amelanotic melanoma (Green, Fortner): left, an untreated control and, right, a similar hamster after treatment with pig skin extract. In the treated hamster tumour regression was accompanied by ulceration.

In most of this work extracts of pig skin (prepared by N. V. Organon) were used in the form of a partly purified 71–80 per cent ethanol fraction[5]. This preparation was known to contain both the epidermal chalone and the melanocyte chalone. The first experiments showed that, with the doses used, squamous cell carcinomata induced in mouse epidermis with benzpyrene were not affected by subcutaneous injections of the skin extract. Further variations on this experiment are required before a conclusion can be drawn.

Experiments were then carried out using Harding–Passey melanomata transplanted into NMRI mice and amelanotic melanomata (Green, Fortner) transplanted into Syrian hamsters. In both cases animals bearing melanomata which had grown to the size of a cherry were injected subcutaneously at a site opposite to the tumour. In both cases, too, each animal was injected daily for 5 days and the total dose given during this period ranged from 25 to 400 mg of the ethanol fraction. With the optimum doses (mouse, 100–200 mg; hamster, 200 mg) both tumours responded in the same way. They became soft and necrotic, the amelanotic melanomata darkened, and then they regressed and ulcerated, and the wound finally healed. With the lower doses there was a partial response while the highest dose proved to be toxic. Evidently this was due to the impurity of the skin extract and partly to the speed and massive scale of resorption of the tumour proteins.

The actual results were as follows: in seventy-five mice receiving either 100 or 200 mg of skin extract all the melanomata regressed completely (Fig. 1) as compared with no spontaneous regressions in more than 1,000 untreated mice with similar cherry size tumours; in 200 hamsters receiving 200 mg of skin extract all the melanomata regressed completely (Fig. 2) as compared with no spontaneous regressions in more than 3,000 untreated hamsters with similar tumours. Subsequently, in most

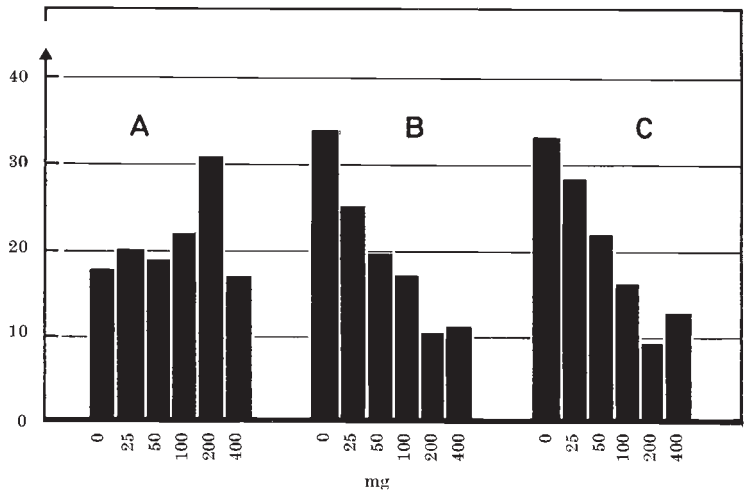

Fig. 3. Results, expressed according to the Friedman nonparametric analysis of variance, of an experiment with hamsters bearing the amelanotic melanoma. *A*, Length of life; *B*, tumour volume; *C*, tumour weight. The control groups 0 were untreated while the groups to their right received respectively 25, 50, 100, 200 and 400 mg of pig skin extract.

of the mice and all the hamsters tumours or metastases recurred, but eight mice were alive and free of melanoma 10 months after the end of the experiments. It remains to be determined whether with treatment for longer than 5 days such recurrences can be prevented. The results obtained with hamsters are also illustrated in Fig. 3.

The question of the identity of the active agent then arose. It was shown that it was not the epidermal chalone, for, when the skin extracts were highly purified by electrophoresis and dialysis[5] and used in equivalent doses, they were not active against melanomata *in vivo* and *in vitro*. Liver extracts also had no effect. The results were apparently not caused by the stressful action of the treatment : necrosis at the site of injection was simulated by skin burnings without any effect on the tumours. Spores of anaerobic bacteria, which might lead to tumour regression as reported by Möse[6], were excluded as causative agents morphologically and microbiologically. Also, because of the fast reaction time, a primary immune response was probably not involved. Injection of EDTA did not influence tumour growth, thereby excluding a possible chelating action of the skin extracts. Finally, it was shown that the skin extracts, in the same doses as were used with the melanomata, had no effect on Walker carcinoma in rats, KG-13-plasmocytoma (Garcia, Baroni, Rappaport) in hamsters, or mastocytoma (Furth) in mice.

The obvious possibility is that the melanocyte chalone may be the active agent. Bullough and Laurence (see previous communication) have shown that both the melanomata used here contain this chalone, and if this is indeed the active agent then, paradoxical as it may seem, extracts of these melanomata should be able to destroy these melanomata. Aqueous extracts of large numbers of Harding–Passey melanomata were prepared in the usual way and these were injected into hamsters with amelanotic melanomata. The preliminary results proved to be similar to those already obtained with skin extracts.

These experiments represent the first application of the chalone concept to the practical problem of tumour destruction, and although final proof is lacking, it is reasonable to suggest that the melanocyte chalone may have been responsible for the results obtained. Whether other types of tumour will respond similarly to the chalones of their original tissues remains an open question.

One final comment is necessary. Later attempts to produce active skin and melanoma extracts have sometimes failed. It seems that the active substance is unstable or that it is otherwise lost during preparation, and that the present methods of extraction are not ideal. Attempts are now being made to devise new extraction techniques.

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Implications of Shock Effects in Iron Meteorites

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The shock loading history of iron meteorites seems to alter profoundly their solid state response to annealing at moderate temperatures. This permits certain conclusions about the history of these iron meteorites to be drawn.

It is well established that iron meteorites are derived from material that was subjected to high temperature processes. Following a period of slow cooling to quite low temperatures the meteoritic parent bodies were fragmented by mutual collision. At some time after their initial slow cooling some of these meteorites have been reheated and, because of the collision-induced stresses in them, extensively altered. Processes such as close approach to the Sun and ablation in the atmosphere, however, have been considered as very unlikely to cause extensive alteration