the practical training the candidate has undergone rather than give too much weight to his mastery of multiple facts and divergent opinions.

A Need of To-day

To turn to another facet of the Hunterian heritage—we all probably accept the truth of Lawrence's aphorism, "Thus we find at last the difference between physic and surgery is a distinction not in science but in practice." Mr. Victor Bonney in his eloquent oration of 1942 made out a strong case for some integration of the many specialties into which medicine of to-day is breaking up. Beyond this there is the need for some corporate body to direct and in some degree associate the multiple activities of medical minds of to-day. If some such joint association is not made effective there is a risk of the all-embracing State machine taking too great a part in controlling our activities. The need for some such organization was envisaged as long ago as 1905 by Sir Clifford Allbutt in his lecture, "The Historical Relations of Medicine and Surgery"; in that he formulated a plea for the foundation of an Academy of Medicine and proposed for it the Wriothlesley motto of "Ung par tout et tout par ung." His ideas, I think, in some degree helped to advance the establishment of the Royal Society of Medicine; but this great foundation, successful as it is, does not supply the basis for that spiritual integration in an organized manner which is desirable if we are to present an undivided mind in face of State control and prevent the fragmentation of medicine into progressively smaller groups.

Duke-Elder in 1942 wrote, "British medicine in its present uncoordinated state, lacking central stimulation, guided by unrelated and often competing professional bodies and administered by a dozen Ministries, is in no position to assert itself in an integrated manner to confer the benefits it might upon the population, or to implement the opportunities of the immediate future in reconstruction, research, and international influence." This may exaggerate the incoherence of our present state, but, even if we reduce his dozen Ministries to one or two, it is not so far off the truth. In 1945 Duke-Elder again returned to the subject. He doubted the power of the Royal Colleges to fulfil their proper function if they remained separate and in some degree isolated, and he put the question: "If the practice of medicine becomes more and more an affair of the State, is the profession provided with a body powerful enough to preserve the soul of medicine in its personal and creative aspects without which it cannot live?"

Many members of this and the other Royal Colleges have, I know, felt the need of some such linking of the existing traditional organizations. Practical propositions were launched some years ago with great hopes, but unfortunately they foundered on the shoals of finance and divided counsels.

One cannot but feel that the spirit and heritage of Hunter, his great museum and our library, do constitute a focal point towards which a renewed effort might be directed to bring our forces together before we are utterly fragmented.

Conclusion

In accordance with the Orator's traditional privilege, I have strayed from my main subject, but I wished to show that the inspiration of Hunter was for the whole body of medicine, that the harvest he sowed matured slowly and has been but gradually garnered. If we look back on Hunter's work I think we may agree that he

conformed to Francesco de Sanctis's definition of the man of science: "He is the highest and most virile type who needs no cult, for he carries the sentiment within him; he has no need for external stimuli for medals and titles, rewards or punishments . . . because he feels more powerful stimuli within him, and his conscience is stronger than any flag or banner."

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RELATION OF SHOCK, CARBOHYDRATE UTILIZATION, AND CORTISONE TO MITOTIC ACTIVITY IN THE EPIDERMIS OF THE ADULT MALE MOUSE

BY

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Green and Bullough (1950) showed that following hind-limb ischaemia or the injection of adenosine triphosphate (A.T.P.) there was an early and strong reduction, or complete suppression, of mitotic activity in the skin of the mouse. This powerful inhibition was shown to occur in the presence of a hyperglycaemia which in normal mice is associated with an increased mitotic rate (Bullough, 1949a). Thus we found further support for the hypothesis which one of us (with H. B. Stoner) had gradually evolved, that the state of shock is fundamentally a profound interference with carbohydrate utilization. It therefore became interesting to find what substances known to be operating in the shock mechanism, or, on the other hand, known to interfere in one or more stages of carbohydrate breakdown, were capable of inhibiting mitosis in the epidermis of the mouse. The typical feature of this action and those now to be described is that the affected cells cease to go into prophase though those already in it complete their divisions normally. The general methods have already been described (Bullough, 1948; Green and Bullough, 1950) and we can therefore proceed directly to the findings.

Hormones Released in the Response to Injury

It was suggested that, in view of the protective role of the suprarenal cortex in the response to injury, a hormonal factor from this source might be responsible for the mitotic inhibition found in shock (Green and Bullough, 1950). In an article suggesting a possible mode of action of A.C.T.H. in allergic conditions (Green,

1950) it was stated that A.C.T.H. had in fact a potent antimitotic effect. At the moment that statement must be modified in so far as all batches tested have not shown this property. We have reason to think that this lack of antimitotic effect reflects some general loss of biological activity. However that may be, there is no doubt that the more stable substance cortisone has a consistent and most powerful antimitotic action on the skin epithelium of the mouse (see Table).

some of its antimitotic effect by causing discharge of cortical steroids, adeny compounds in general have a direct antimitotic effect, or at least one not mediated through the suprarenal. Adenosine, though less active in this respect than its phosphorylated derivatives, causes a fall in general oxygen consumption and a transient fall in body temperature (Green and Stoner, 1950). Does adenosine, therefore, exert its antimitotic action by interfering in the respiratory cycle of carbohydrate utiliza-

Changes in the Epidermal Mitosis Rate of Mice (Kreyberg "White Label" Males) after Various Treatments

No. of Mitotic Cells in 10 cm. of Ear Epidermis Cut 7 μ Thick

Dose mg/10 g. Body Wt.	Cortisone	Controls	Dose mg/10 g. Body Wt.	Adrenaline	Controls	Dose mg/10 g. Body Wt.	Adenosine	Controls
0.1	12 (7-21)	53 (40-69)	0.004	6 (3-13)	—	3	14 (8-24)	68 (54-86)
0.5	0 (0-4)	88 (71-108)	0.01	20 (13-31)	—	3	20 (13-31)	82 (66-102)
1	13 (8-22)	56 (43-73)	0.02	0 (0-4)	—	3	12 (7-21)	110 (91-133)
2	0 (0-4)	52 (40-68)	0.04	2 (0-7)	62 (48-79)	3	6 (3-13)	60 (47-77)
2	0 (0-4)	98 (80-119)	0.04	0 (0-4)	85 (67-106)	3	0 (0-4)	76 (61-95)
2	0 (0-4)	—	0.04	5 (2-12)	62 (48-79)			

All the drugs were administered intraperitoneally at 10 a.m. G.M.T. Control animals received an equivalent volume of 0.9% saline. All the counts were done on pieces of ear epidermis obtained at 2 p.m. G.M.T. Figures in brackets represent the 95% confidence intervals for the expected number of mitotic cells in 10 cm. (calculated on the basis of a Poisson distribution—that is, they give bounds to the purely chance variation of the number of mitotic cells counted).

Fairly strong inhibition was observed with parenteral doses of 0.1 mg. per 10 g. mouse. There is little doubt that some effect will be observed at a still lower dosage, for local painting of the cortisone suspension (25 mg./ml.) on one ear was sufficient to cause not only complete suppression of mitosis in the treated ear but also strong inhibition in the opposite ear.

As there is some evidence that adrenaline is one of the intermediary agents in the pituitary-adrenal response to injury (Long, 1947, 1949) and following A.T.P. injection (Stoner and Green, 1950) its effect was also studied, and it was found that it too depresses epidermal mitosis quite profoundly (see Table).

Other Substances Possibly Concerned in the Mechanism of Shock

Of these, A.T.P. and its derivatives most concern us here, for A.T.P. is known to have an antimitotic effect (Green and Bullough, 1950). The question remained open whether this was a specific property of the compound or one of the many reflections of its shock-inducing action with a concomitant stimulation of the pituitary-cortical mechanism (see Stoner and Green, 1950). To our surprise adenosine proved to be a powerful antimitotic agent *in vivo* in doses so far below the shock-inducing dose that little question of this being a non-specific action seemed possible (see Table). Moreover, Hughes in a personal communication stated that in tissue culture chick embryo fibroblasts showed a similar response both to adenosine and to adeny compounds, which in biological concentrations prevented cells entering into the prophase of mitosis. Nor, on other grounds, did it seem likely that the effect of adenosine itself in the whole animal was due to the liberation of a cortical steroid with the antimitotic activity of cortisone; for adenosine, at the active antimitotic dosage, is unlikely to cause any significant suprarenal cortical discharge, at any rate in the rat (see Green and Stoner, 1950). Still more apposite is the fact that the skin of the adrenalectomized mouse responds to the antimitotic action both of adenosine and of A.T.P. (results will be published later).

We are left, therefore, with the provisional conclusion that, while A.T.P. injection in all probability exerts

tion? Cortisone does not depress the body temperature but has a very powerful antimitotic action, and interference with the phosphorylation of sugar in the early stages of its glycolytic breakdown could explain this action.

What evidence is there that other agents capable of inhibiting any stage of carbohydrate breakdown interfere with mitosis? In tissue culture Hughes (1950) has reported on a variety of mitotic inhibitors, but only two—iodoacetate and fluoride, both inhibitors of glycolysis—completely suppressed mitosis in pre-prophase. Sodium fluoracetate, a powerful inhibitor in the carbohydrate respiratory cycle (see Peters, 1948), did not suppress mitosis in pre-prophase. *In vivo*, however, we have found in some preliminary experiments that all the three substances—sodium fluoracetate, sodium pyrophosphate, and iodoacetic acid—tested because they inhibit different phases of carbohydrate metabolism, showed mitotic inhibition in the pre-prophase stage.

Conclusions

In a preliminary report of this kind we would draw only general conclusions. The results tend to show that any significant interference with carbohydrate utilization at any stage, in the intact animal, prevents the epithelial cells of mouse skin from entering into the first stage of mitosis, possibly because all the energy build-up responsible for mitosis takes place in the pre-prophase stage (Bullough, 1949b). If this is so it provides supplementary evidence to the much more numerous and direct data (now being assembled) by the Sheffield Traumatic Shock Team suggesting that the state of shock is one of profound interference with carbohydrate utilization. It seems highly probable that the antimitotic effect of shock-inducing measures is due to this interference. The effect seems to be due in part to the liberation of a cortical steroid(s) which may interfere, possibly in the early stages, in the glycolytic breakdown of carbohydrate. Strong as this inhibition may be, judging from the antimitotic action of cortisone, it could not be the only way in which carbohydrate utilization is affected in the shock state, for, while A.C.T.H. and cortisone do not seriously affect the metabolic rate of the whole animal, a striking reduction in this rate is a cardinal feature of the shock state.

A working hypothesis on the basis of these mitosis counts is that in shock there are at least two inhibitory mechanisms affecting carbohydrate catabolism—one operating hormonally in the stage of glycolysis, and the other operating (possibly through the direct action of adenylyl compounds) in the oxidative cycle. Stoner, Green, and Threlfall (1950) have already provided some chemical evidence of an interference with carbohydrate utilization in shock. Here we are mainly concerned to show how these studies may help to explain one aspect of the complicated action of cortisone and related steroids.

If the antimitotic effect is, as seems very likely, exerted on other tissues, such as the reticulo-endothelial, and in other species than the mouse, this powerful action must play a part (see Green, 1950) in the anti-allergic, anti-inflammatory, and anti-repair effects which in the mouse and rabbit, and possibly man, are so prominent. That such effects are incidental and not in any way linked up with the known therapeutic effects of cortisone and related substances is most unlikely. That they explain all the therapeutic effects is still less likely, for in that case adrenaline or A.T.P. should, in appropriate dosage, have the therapeutic virtues of cortisone, which they manifestly have not. The antimitotic effect of adrenaline is, however, interesting in view of its rather similar effects to A.C.T.H. and cortisone in reducing or abolishing some hypersensitive tissue reactions. This particular property is possibly due to the discharge, in excess, of a cortical steroid through adrenaline stimulation via the pituitary-adrenal route.

Summary

Cortisone, injected or applied locally, is a powerful inhibitor of mitosis in the pre-prophase stage in the epidermis of the adult male mouse.

Two other substances possibly concerned in the shock reaction—adrenaline and adenosine—when injected in adequate dosage have a similar action.

It is shown that these findings give indirect support to the hypothesis that in the shock state there is a profound interference with carbohydrate metabolism.

We are indebted to the Medical Research Council Committee on A.C.T.H., Cortisone, and Related Substances for supplying the cortisone, and to Mr. R. F. Wrighton, of the Department of Social Medicine, Sheffield University, for his valuable statistical help.

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Fresh water aboard ship has always been something of a problem, and its magnitude can be gathered from the fact that a modern liner uses about 220 tons a day in the Tropics, and must provide storage for 3,000 tons, representing a great loss in cargo capacity. The P. & O. are now for the first time to make all their fresh water by continuous distillation of sea water. In their new *Himalaya* special evaporators have been designed for heating by steam taken from the turbines after it has done its useful work there.

SHOCK AND NEOPLASIA

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It was shown (Green, 1949) that in the rat the growth of neoplasms from the time of transplantation was unaffected, or relatively unaffected, by repeated induction of the shock state, a procedure which powerfully inhibits mitosis in normal epidermis and probably many other tissues (Green and Bullough, 1950). This was unexpected, since the pronounced fall in oxygen consumption in the tissues of the shocked animal (Green and Stoner, 1950) and some retardation of general body growth might have been expected to retard neoplastic proliferation somewhat. Preliminary evidence was presented at the International Cancer Congress in Paris (Green, 1950) that, as might now be expected, the mitotic rate of the cells of the transplanted tumour was relatively unaffected by such a strong shock-inducing measure as hind-limb ischaemia or by the injection of A.C.T.H. Some further details are now presented together with an interesting extension of this inquiry. The general methods used have already been described (Bullough, 1948; Green and Bullough, 1950).

Tumour Mitosis and Natural Antimitotic Agents

Since then further investigations make it clear that such strong antimitotic agents as the shock state or injected cortisone (Green and Ghadially, 1951) do not affect mitosis in various transplanted tumours of mice and rats to anything like the same degree as is observed in the epithelium of normal skin.

In Table I some figures are abstracted from two typical experiments to show the effect and time-relationships of ischaemic shock and cortisone injection on the mitotic

TABLE I.—Effect of Ischaemic Shock and Cortisone on Epidermal Mitotic Rates. Average Number of Mitoses per 10 cm. Length of Ear Epidermis in Sections Cut at 7 μ . The Figures Given are for 5 Strong's CBA Male Mice, and in the Case of Cortisone for 5 Kreyberg's "White Label" Male Mice

Time of Day	Untreated Normal Mice	Ischaemic Shock. Removal of Limb Tourniquets at 11.30 a.m.	Cortisone, 0.2 mg. I.P. Injected at 12 noon
10.30 a.m. ..	31 $\pm$ 2.2	27 $\pm$ 2.9	—
12 noon ..	52 $\pm$ 4.1	14 $\pm$ 1.1	58.8 $\pm$ 14.2
1.30 p.m. ..	73 $\pm$ 1.2	0	9.2 $\pm$ 7.0
3 p.m. ..	44 $\pm$ 1.2	0	6.5 $\pm$ 3.0

rate in the skin of normal mice. In Table II the effect of similar treatments in tumour-bearing mice and rats on the mitotic rates of the tumours and of the epidermis in the same animal is illustrated. It has been found difficult in some instances to determine the effect of antimitotic agents on the skin of tumour-bearing mice, and the presence of a rapidly growing neoplasm may conceivably depress the rate of mitosis in normal epidermis. This point, however, is being investigated further, for, if true, it could be important. It will be readily seen, particularly if Tables I and II are compared, that the tumour mitotic rate in both the mouse and the rat is relatively unaffected as compared with the epidermal rate, either by ischaemic shock or by cortisone injection.