at being shown the admission ward after his recovery and also from his expressed lack of surprise at seeing his family grown up after four years. This hypothesis would almost demand an organic cortical inhibition, as the stupor remained so stable for such a long period and completely resisted superficial attempts to break it down. In this connexion, it would have been helpful to be able to relate the anaesthetic given the patient at the time of his operation to the beginning of the psychosis, but there was a period of four days after the operation in which the patient appeared normal.

Finally, where was the gain, real or imagined, that the classical hysterical breakdown demands? There was certainly no real gain, and there seemed to be no intolerable situation to escape from, except, possibly, the delusional wickedness of the patient's own creation.

Conclusion

The lack of opportunity to try less dramatic methods of treatment before electric convulsion therapy precludes any definite conclusions, but the weight of the evidence supports the hypothesis that this reaction was depressive in type.

While bearing in mind the undesirability of trying to classify psychiatric material too closely, the aetiology of a state that seemed to have become stabilized, and the possible further duration of this state without treatment, become fascinating problems. It seems sufficient to show that the reaction was not hysterical and to leave the subject with the tentative suggestion that a generalized psychic inhibition with a reversible organic basis seems indicated. The "protective" cortical inhibition described by Pavlov (Sargant, 1951), protective in this case from the intolerable delusional ideas of the patient, might well be the aetiological basis of this prolonged stupor, and would certainly account for the prolonged amnesia, the stable state of stupor, and its relatively rapid and complete response to electric convulsion therapy.

Summary

A case of stupor of over four years' duration is described, with its rapid and complete recovery—apart from a complete amnesia for the period of the stupor and a short preceding period—following electric convulsion therapy.

The case is discussed, and it is suggested that its aetiology may be similar to that of the generalized "protective" cortical inhibition described by Pavlov.

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A pamphlet just issued by H.M. Stationery Office deals with education during National Service. The War Office offers considerable facilities for Servicemen wishing to prepare themselves for civilian occupations during their off-duty time. As well as correspondence courses and the possibility of attending evening classes at polytechnics and the like, there are special higher education centres at Aldershot and Catterick in this country, and abroad in Germany and the Middle East and Far East. Biology and chemistry are among the two dozen subjects offered at these centres.

CORTISONE AND TUMOUR GROWTH

BY

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Green (1950) postulated, on the basis of the inhibitory action of A.C.T.H. and cortisone on epidermal mitosis (Green and Savigear, 1951; Green and Ghadially, 1951), a hypothesis of their mode of action in rheumatoid arthritis and other hypersensitive states. This was that antibody formation was retarded, not by some direct chemical antagonism, but because the very-short-lived antibody-forming mesenchymal cells were not being replaced. The well-known involution of lymphoid tissue, for instance, became from this standpoint not a "degenerative" but an aplastic process.

We have not yet seen in immunological studies with cortisone any evidence which would exclude this hypothesis, and we now have some further evidence in its favour in transplantable cancer studies. It was shown (Green, 1951) that the shock state (and therefore, presumably, cortisone-like steroids) did not affect transplanted sarcoma growth, and (Green and Savigear, 1951) that mitosis in the precancerous epidermal cell, unlike the normal cell, was not strongly inhibited by shock or by cortisone treatment.

With these facts in mind it seemed possible that cortisone might in fact facilitate rather than retard transplanted tumour growth by diminishing antibody formation. This was shown to be so quite convincingly. Strong depression of homologous immunity, in this case to rat sarcoma iso-antigens, was readily achieved. About 40% of sarcomata (Rb/1) growing in a strain of Wistar rats different from its normal host strain regress completely at some stage. In five out of eight of such rats following systemic treatment with cortisone acetate (20 mg. subcutaneously daily for four days) vigorous growth was resumed. The responsive tumours weighed at the time of treatment from 5 to 20 g. (roughly estimated) and had been regressing strongly for from 7 to 14 days. Renewed growth was always obvious seven days after beginning treatment, and continued until the rat was killed by the tumour. This chemically induced sarcoma has never behaved spontaneously in this way during many years of transplantation. The three failing to respond were all small hard nodules (not more than 1 by 0.5 cm.), and as they continued to be rapidly absorbed it is likely that they did not now contain viable sarcoma cells.

Rat-to-Mouse Transplantation

Depression of heterologous immunity in two strains of mice was then attempted. Two of six mice developed microscopic invasive growths when given rat sarcoma (Rb/3) mince mixed with 0.04 ml. (1 mg.) of cortisone suspension followed by systemic treatment with cortisone acetate (0.5–1.5 mg. subcutaneously for 7–10 days). In the remaining four mice, as in the six controls, the inoculated cells did not survive, let alone grow. A further group of four CBA mice, similarly treated except that cortisone was not added to the tumour mince, showed no survival of the implant.

However, when the technique was altered so as to include pretreatment with cortisone a conclusive result was obtained. Cortisone was injected (1 mg. subcutaneously daily for four days) before the implantation (both subcutaneous and intra-peritoneal) of 0.05 ml. of tumour mince mixed with 0.04 ml.

of cortisone (1 mg.) suspension. This was followed by further cortisone (1 mg.) injections for 10 days. Eight of nine surviving mice (four Kreyberg and five CBA) showed microscopic "takes" and four showed definite tumour masses at from 6 to 20 days, when at intervals they were killed or died. Mice showing the most prominent growth of tumour tissue were usually ill, and often died spontaneously. In a second group, similarly treated, seven of eight survivors showed microscopic takes. In none of the 13 and nine controls was a take recorded.

Microscopically it was evident that the tumour cells in most of the treated mice had continued to proliferate locally and invade peripherally into adjacent tissue, including the intestinal wall. The degree of invasive growth was greatest in the mice dying spontaneously, and was therefore related presumably to the animals' sensitivity to the toxic action of cortisone. In contrast none of the 22 control mice showed any histological evidence that the grafted tumour cells had proliferated; instead they had become necrotic and attracted a dense lymphocytic and mononuclear cell response, the dead tissue being partially organized by the sixteenth day. At this time the treated mice showed invasive proliferation with strikingly little evidence of cellular reaction in the surrounding tissues. By the twentieth day, however (10 days after the cortisone treatment ceased), an early reaction to the more central necrotic mass of cells in the original implant was evident.

Attempts to obtain the same result by treatment with A.C.T.H. instead of cortisone were not successful in a small group of four mice. They were pretreated for four days with 1 unit twice daily, followed by a further four days' treatment after transplantation. In none was there any growth of sarcoma cells.

Fowl-to-Pigeon Transplantation

With the aid of cortisone definite growth of the Rous fowl sarcoma in the pigeon has been attained in one instance. The first attempt, corresponding to the original rat-mouse experiment, was a relative failure. Of eight pigeons implanted with sarcoma mince mixed with cortisone (10 mg.), followed by 10 mg. of cortisone daily for 14 days, only one doubtful take resulted. However, in a further group of three pigeons pretreated with 25 mg. of cortisone daily for four days and further treatment similar to the previous group there was progressive tumour growth in one bird resulting in a firm white intramuscular mass (5 by 3 by 2 cm.) at five weeks. This was transplanted into a further group of six pigeons, three with cortisone and three without, but in none did a take result.

Transplantation of Human Neoplasms into Mice

Having obtained positive results with animals, we attempted to transplant human neoplasms into the mouse, using the same technique as in the previously successful experiment. Up to date we have one positive result to report with an "oat-celled" bronchogenic carcinoma. Of 12 cortisone-treated mice (six CBA and six White Label) five showed microscopical evidence of non-invasive tumour growth at the periphery of the implant, when killed or dying at from 6 to 16 days. As always in cortisone-treated animals, there was no cellular reaction around the tumour implant, contrasting with a very considerable reaction in the control mice. A similar experiment with a highly differentiated hypernephroma failed.

Heterologous and Homologous Immunity

These results show that cortisone strongly depresses antibody production to iso-antigens and heterologous antigens in transplanted tumour tissue. The almost complete failure of a local cellular reaction also indicates that this depression is due to a large reduction in the number of the antibody-producing cells concerned. This may be due to mitotic

inhibition in cells of lymphoid origin such as we have shown to occur in basal epidermal cells, or to the "lytic" action of cortisone on such cells. It is obviously vital for successful transplantation that this reduction should be achieved before heterologous tumour cells are implanted. With the short-lived cells of the lymphoid series, failure to reproduce would rapidly deplete their numbers and leave the host at the time of transplantation without an effective defence. The fact that whole-body irradiation with x rays is one of the few relatively successful methods of diminishing heterologous immunity to tumour transplants favours this explanation, for it is generally believed that the same treatment is in essence directly, or indirectly, antimitotic to the antibody-forming cells. To what extent this defence depends on local or systemic antibody production cannot be assessed, but the absence of a local cellular reaction and the possibly greater reduction in heterologous immunity when cortisone is present in the tumour inoculum suggest that local resistance cannot be ignored, at least in the early stages. The failure of A.C.T.H. treatment to reproduce the effects of cortisone on heterologous tumour growth may also be of relevance here.

Billingham, Krohn, and Medawar (1951) have shown that cortisone, applied locally or injected systemically, lengthens the life of skin homografts mainly by retarding the development of systemic immunity to them. They do not attempt an explanation of the mechanism of this or of why local treatment is much more effective than general at the same dosage. Whatever the explanation, it is obviously very similar to that for the present findings with homologous and heterologous tumour transplants.

Application of the Technique

Perhaps the most generally interesting aspect of our work is that it points to the possibility of a simple method of tumour transplantation from man to animals which might have diagnostic value in undifferentiated neoplasms if they differentiated in the transplanted state. It would in any case open up a method for testing therapeutic agents on human tumour cells. Our more recent experiments suggest that cortisone is, in the present context, by no means the most powerful of the cortical steroids, and it is quite possible that progressive growth of highly malignant human tumours will be regularly achieved with the use of more potent steroids alone, or, if not, combined with general x-irradiation. Experiments to this end are in progress.

Another possible application of this technique now being studied is the analysis of the mode of action of chemotherapeutic agents on transplanted tumours and the influence of immunity processes on metastatic spread. All these findings, together with the lack of growth-inhibiting effect of cortisone on precancerous and many types of cancer cells, make cortisone and related steroids a most welcome extra tool for probing cancer mechanisms.

Summary

Strongly regressing transplanted sarcomata in rats progressively grew, with a fatal outcome, following systemic treatment with cortisone.

With pre- and post-transplantation systemic treatment with cortisone, aided possibly by the addition of cortisone to the tumour inoculum, successful growth of some malignant tumours from rat to mouse, fowl to pigeon, and man to mouse was achieved.

This reduction of homologous and heterologous immunity to tumour growth provides another example of the strong immunity-lowering properties of cortisone. The evidence favours the view that this effect is due to the antimitotic action of cortisone on antibody-producing cells.

Possible practical outcomes of these findings are discussed.

We are indebted to the Medical Research Council Committee on A.C.T.H., Cortisone, and Related Substances for supplying the A.C.T.H. and cortisone.

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ABSENCE OF RESPONSE TO CORTISONE

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Complete absence of clinical response of rheumatoid arthritis to massive doses of cortisone is rare, though relative lack of response is not uncommon. The following case, which failed to respond to 500 mg. of cortisone a day, 100 mg. of A.C.T.H. intravenously, or to hydrocortisone ("compound F") intra-articularly, answers some of the questions raised in the annotation in the *British Medical Journal* of May 10 (p. 1016), discussing the paper by Kellgren and others on the same subject (p. 997).

Case Report

The patient was a man aged 38. A brother had had rheumatic fever.

FIG. 1.—Showing the effect of A.C.T.H. and cortisone on the circulating level of 17-hydroxycorticosteroids ($\mu\text{g.}/100$ ml. plasma), on the urinary excretion of 17-ketosteroids and neutral reducing lipids, and on circulating eosinophils.

January, 1949.—Acute rheumatoid arthritis started in the left wrist, and shortly afterwards both ankles became involved. He was treated with gold, which was stopped owing to a slight rash, from which he soon recovered.

August, 1950.—On admission to the Royal National Hospital for the first time his general condition was good; there was swelling of the wrist and ankles. The sedimentation rate was 27 mm. (Westergren); haemoglobin 94%. Hypoglycaemic treatment was without benefit.

February, 1951.—He was readmitted to hospital in very similar condition: sedimentation rate 26 mm. (Westergren); Wassermann reaction negative; plasma cholesterol, 69 mg. per 100 ml. For a short period 100 mg. A.C.T.H. daily and, later, 200 mg. cortisone daily was given without benefit. Deep x-ray treatment to the feet was without result.

June, 1951.—A slight rash appeared on the legs, from below the knees to above the ankles, and cleared up within a month.

July, 1951.—He was again admitted to hospital. His general condition was still quite good, but affected joints were more painful. The sedimentation rate was 57 mm. (Westergren); haemoglobin, 97%; glucose and insulin tolerance normal. Histamine-fast achlorhydria was present. He was again treated with A.C.T.H., the dosage being increased to 400 mg. a day, given in four doses. There was no decrease in pain or joint swelling or increase in joint movement. The urinary 17-ketosteroids increased slightly, but there was no obvious change in corticoids. After a rest period 500 mg. of cortisone was given daily by injection, again with no clinical improvement, but there was a slight decrease in 17-ketosteroids with a slight increase of corticoids. Intravenous A.C.T.H., 20 mg. and then 100 mg., given in eight-hour drips, again produced no clinical effect. Throughout treatment the eosinopenic response was normal, the fall being 70, 77, and 42%. The effect of A.C.T.H. was not potentiated by ascorbic acid or thyroxine. There was no clinical evidence of adrenal insufficiency, and the Kepler test gave a normal result.

March, 1952.—The patient's condition had definitely deteriorated, his hands, wrists, elbows, feet, ankles, and right jaw being affected. The sedimentation rate was 23 mm. (Westergren); haemoglobin, 87%. Thyroid function was investigated, using I^{131} , and was found to be within a low range of normal. (Slope uptake 1.3×10^{-2} ; 48-hour excretion 51.2%; thyroid index 2.6). The 17-ketosteroids were 8.3 mg. in 24 hours.

Two injections of 2 ml. (50 mg.) intra-articular cortisone into the left wrist gave no relief of symptoms, and then two injections of 50 mg. of hydrocortisone were given into the same joint, again without any benefit. There was no depression of the circulating eosinophils.

April, 1952.—The patient was transferred temporarily