DR. R. N. MAINI (*London*) How did you diagnose systemic sclerosis and was there any information on antinuclear factors available on any of these patients?

DR. ROWELL All the patients had Raynaud's phenomenon followed by characteristic cutaneous changes and multisystem involvement of systemic sclerosis. Antinuclear factor was done on all cases. There was no consistent pattern to suggest any relation between antinuclear antibodies and the pattern of staining seen in the sections. All this series had one or more antinuclear factors. It has been shown that nearly 70 per cent. of patients with systemic sclerosis have antinuclear factor of one pattern or another (Rowell and Beck, 1967).

DR. G. HUGHES (*London*) I should like to ask you again about your controls, because this sort of straining is not specific. The second point is that mesangial deposition is found in patients with systemic lupus without clinical evidence of renal disease and is of uncertain significance.

DR. SCOTT I agree. In our study, too, mesangial staining had little clinical significance. The question is why is this so? Are there two different types of complexes involved in systemic lupus erythematosus, one which lodges in or on capillary basement membranes and one which lodges in the mesangium? As to the controls used; the antiglomerulus conjugates were absorbed with normal human serum and Group A and B red cells before use. The usual blocking procedures were run in parallel with staining experiments. The staining seen in the systemic sclerosis and systemic lupus erythematosus material was compared with that seen in sections of normal kidney.

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Occurrence of DNA-antibodies in Antinuclear Factor containing Sera and a Comparison with Immunofluorescence. By D. N. GLASS, J. CAFFIN, H. J. ANDREWS, R. N. MAINI, and J. T. SCOTT (*Kennedy Institute of Rheumatology and Charing Cross Hospital*)

HeLa cell C_{14} DNA at a final concentration of 0·5 μg./ml. was used in a 'Farr' type ammonium sulphate assay for the detection of DNA binding in ANF positive sera. The sera had been obtained from a range of connective tissue diseases including systemic lupus erythematosus (SLE). ANF was detected by the usual immunofluorescent technique using rat liver sections. Of the 150 ANF positive sera tested, 25 showed raised DNA binding correlated with clinically active SLE.

The relationship of DNA binding to ANF tested at serum dilutions of 1:10 and 1:1,000 is shown below:

DNA binding	*No. ANF positive at a dilution of:*	
	1:10	1:1,000
Positive	25	9
Negative	125	17
Total sera	150	26

Eleven out of 26 sera with ANF at 1:1,000 dilution were derived from patients with SLE and of these seven were positive and four negative for DNA binding. Two other sera with ANF from non-SLE patients gave low DNA binding values and were negative on repeating the test. It will be noted that there was a better correlation between DNA binding and sera positive for ANF at a 1:1,000 dilution than at 1:10. 25 DNA antibody positive sera gave homogenous pattern fluorescence in most instances and comet or membraneous in the rest. No particular pattern of fluorescence correlated specifically with DNA antibodies, each pattern also being found in DNA antibody negative sera.

DNA of high purity (containing RNA protein contamination of less than 0·1 per cent.) gave very similar results to those obtained with the crude DNA preparation. DNA from other sources (kindly supplied by Dr. H. Harley, University College Hospital Medical School) such as CVI (monkey) cells was also undertaken and the results were comparable. However, the ammonium sulphate precipitation technique has several unsatisfactory aspects for routine use. The technical problems include a necessity to work at 4°C. for separation and difficulty in centrifuging down the whole of the rather fragile ammonium sulphate precipitation, giving an unsatisfactory extrapolation of results by having to count the upper half of the supernatant as well as the remainder of the precipitate and supernatant. The latter occasionally gave rise to DNA binding with a negative value. A lack of precision due to large replicate variation between duplicate samples, especially at the low level of binding, was noted and accounted for values above the normal range (false positives) in normal sera. For some investigative and research purposes a more precise assay is necessary, and a double antibody technique developed in this laboratory might be suitable.

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A Study of Depression in Rheumatoid Disease. By G. ZAPHIROPOULOS and H. C. BURRY (*Department of Rheumatology, Guy's Hospital, London*)

It has long been suggested that patients suffering from rheumatoid disease may suffer a mild depressive reaction which can materially impede their progress and delay rehabilitation.

We have endeavoured to determine the incidence of depressive reaction in patients suffering from rheumatoid disease admitted for in-patient therapy to the Hume-Kendall Unit at New Cross Hospital. For the purpose of this study the Beck Depression Self-Assessment Inventory was used. This is designed to incorporate all symptoms relevant to the depressive constellation of symptoms, at the same time providing for grading of the intensity of symptoms. With this method the highest score (26–45) corresponds to the clinical rating of 'moderate to severe' degree of depression, the middle range (15–25) to 'mild to moderate', and the lowest range (0–14) to 'no-depression'. Symptom complexes which could have had a physical rather than psychological basis were not scored, *e.g.* work inhibition, weight loss, or loss of libido.

Fifty unselected patients with rheumatoid disease fulfilling the A.R.A. criteria for definite or classical RA were included in the study. They completed the inventory

within 3 days of admission after the purpose of the assessment had been clearly explained to them. 26 of these patients agreed to complete the inventory again at the time of their discharge. A control group of 32 patients suffering from a variety of chronic painful non-inflammatory diseases of the locomotor system were also studied from amongst patients admitted to the same unit. The two groups were reasonably well matched, but the duration of disease was longer in the rheumatoid disease group than in the controls (11 and 4·6 yrs respectively). In the fifty RA patients there were fourteen males and 36 females. Their mean age was 53·6 yrs. In the control group there were ten males and 22 females and the mean age was 50·5 yrs.

Evidence of a depressive reaction was forthcoming in 46 per cent. of the RA patients compared with 18·7 per cent. of the controls. A statistical evaluation of the scores obtained in these two groups gave $t = 2{\cdot}25$; $P < 0{\cdot}05$.

Although there was no significant correlation between the inventory score and the duration of disease, it was apparent that where depression was present it tended to occur rather earlier in the course of the disease amongst men patients and later in the course of the disease amongst women patients. The depressive inventory score appeared to be uninfluenced by the age or sex of the patients, the height of the erythrocyte sedimentation rate, the functional grading, the presence or absence of rheumatoid factor, nodules, or erosions, and the administration of steroid therapy.

An analysis of the results of the 26 patients who completed the inventory a second time, at the time of their discharge, revealed a very highly significant improvement in their inventory score ($P < 0{\cdot}001$). In addition to treatment directed towards their arthritis, five of these patients received antidepressant drugs and eight received tranquillizers. The reduction in score was apparent whether psychotropic drugs were used or not.

This study illustrates the high incidence of depressive reaction amongst patients suffering from rheumatoid disease. The incidence and severity of these reactions appears to bear little relation to the duration or intensity of the disease, they appear to be favourably influenced after a period of in-patient hospital treatment.

Discussion

DR. C. F. HAWKINS (*Birmingham*) Is suicide a complication of this type of depression?

DR. ZAPHIROPOULOS In our experience of these fifty patients, one had committed suicide and one other patient attempted suicide. I believe it is uncommon in rheumatoid patients.

DR. J. M. GUMPEL (*London*) A methodological question. Patients with rheumatoid arthritis are generally very pleasant patients to treat, because they are so grateful for what one is able to do for them. It is important to know, therefore, whether the same person administered the questionnaire at the beginning and at the end of patients' hospital admission, and was that person connected or unconnected with the treatment. A useful control would be a re-administration of the questionnaire 1 or 3 weeks after discharge from the hospital.

DR. ZAPHIROPOULOS At the start the questionnaires were given away by one of the social workers; then I took over the job and gave the majority both on admission and on discharge to the 26 who agreed to complete them. It would certainly be interesting to administer the inventory at shorter intervals both during and after hospitalization and see whether a pattern would emerge. We are in fact thinking in terms of such a study. I think a prospective study of pain and mood patterns has been done (Moldofsky and Chester, 1970). There is, in fact, evidence of quite a great variation in mood from day to day, and even at different times of the day.

DR. A. G. WHITE (*London*) The size of the subgroup who failed to answer the questionnaire the second time is surely such as to raise the possibility that at least some of these, rather than becoming less depressed, might have become more so. Has this been excluded from the study?

DR. ZAPHIROPOULOS They did not actually refuse to complete the inventory. These were human errors—it was not a refusal. The incidence of mood disturbance according to the inventory score was 46·2 in these 26 patients on admission, as compared to 46 per cent. of the whole 50. Again the mean score was 16·6 in the 26, and in the whole group of fifty it was 15·0, remarkably similar, so we thought the 26 patients would make a valid group for comparison.

DR. A. G. MOWAT (*Oxford*) You have drawn attention to how important it is to treat the total patient. We sometimes forget to treat the whole *family*; to run the same sort of inventory for the spouses might be equally useful.

DR. ZAPHIROPOULOS You may have noticed that we did not include any psychosocial studies of these fifty patients.

DR. J. A. COSH (*Bath*) Surely your inventory is based on the patients themselves answering questions. We asked a psychiatrist (Ward, 1971) to make an analysis of patients undergoing treatment at a rheumatic hospital in Bath and he was interested to try and answer the question 'Is the rheumatoid patient different in his makeup from others'. He found that in the early stages of rheumatoid arthritis patients were less neurotic. He compared them not only with ordinary controls but also with neurotic patients who had high scores for neuroticism. This study was made objectively by a psychiatrist and I found his assessments very helpful because he was able to give us some insight into how the individual would react to his disease as time went on. Your study is based on a self-assessment. Do you think this has pitfalls?

DR. ZAPHIROPOULOS I certainly think that ideally our study should have been coupled with psychological assessment by an expert. It was simply an attempt on our part as clinicians to understand these people better and to find out the incidence of depression and other mood disturbance. The theory that rheumatoid arthritis is a psychosomatic disease, that patients are inherently somehow different, is certainly not supported by the findings you quoted.

DR. M. I. V. JAYSON (*Bath*) One further point that came out of Dr. Ward's study and is also held by some of our psychiatrists is that the patient with chronic disability

develops concealed hostility and difficulty in demonstrating feelings of aggression to people around. Is this true and do you think that this is responsible for their depression?

DR. ZAPHIROPOULOS It is true that patients with chronic disability are likely to exhibit 'conflicts in the expression of hostility', but I do not know whether the anxiety and depression is a result of this; they are all part of the general disturbance seen in rheumatoid patients (Robinson, Kirk, Frye, and Robertson, 1972).

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Effect of Corticotrophin and Oral Corticosteroids on nocturnally released Growth Hormone. By R. MOTSON, D. N. GLASS, J. I. EVANS, P. HILL, J. R. DALY, and N. RUDOLF (*Clinical Research Division, Kennedy Institute of Rheumatology, West London Hospital, and Department of Psychiatry, Edinburgh University*)

Corticosteroid therapy in children is associated with dwarfism, although there is uncertainty about the mechanism of this. Chronically administered steroids can inhibit the growth hormone response to insulin-induced hypoglycaemia, but generally only after some years of therapy and without uniformity. It has not hitherto been possible to find an index of growth hormone function which was inhibited by a dose of steroids unless given for more than 2 to 3 days. It is necessary to find a more physiological index for growth hormone before one could relate levels to dose of steroids, rates of growth, or any other metabolic function.

Growth hormone release is now well documented in association with Stages 3 and 4 of slow-wave sleep (Takahashi, Kipnis, and Daughaday, 1968). This sleep-associated growth hormone release appears to be a physiological situation in which one can study growth hormone satisfactorily, and avoids the necessity for artificial stimuli such as insulin hypoglycaemia or arginine infusions which have been used for previous studies of the effect of corticosteroid therapy on growth hormone secretion. We have undertaken a systematic examination of the effects of corticosteroids on nocturnal growth hormone release, and have previously reported the suppressive effect on growth hormone release of a single injection of Depot Tetracosactrin given to normal subjects 16 hours before the onset of sleep (Glass, Evans, and Daly, 1972). Further experience now shows that this effect is not obtained if a single 80 unit injection of ACTH (Acthar gel) is given at a similar time. This dose, whilst containing at least 1 mg. of the porcine ACTH preparation, gives adrenal stimulation for a much shorter period than 1 mg. Depot Tetracosactrin. The mean peak of growth hormone was $37{\cdot}9 \pm 12{\cdot}3$ S.D. in five subjects compared with $27{\cdot}4 \pm 16{\cdot}0$ S.D. in the same subjects during nights when the hormone was not given; the equivalent corticosteroid values being $7{\cdot}7 \pm 1{\cdot}5$ and $6{\cdot}7 \pm 2{\cdot}6$ respectively. In order to investigate whether the effect of Tetracosactrin on growth hormone release was a direct one, or mediated *via* the action of the raised corticosteroid level it produced, we next examined the effect of oral corticosteroids on nocturnal growth hormone release in a group of normal individuals: a single orally administered dose of long-acting steroid (Flucortolone) significantly suppressed the sleep associated growth hormone peaks.

Discussion

DR. B. M. ANSELL (*Taplow*) The team should be congratulated on this difficult work. It is now time to re-think what type of steroid to give to children and when. At this moment it is still difficult to decide and I wondered if there was an urinary method of assessing growth hormone over a 24 hour period, which would be much more practicable for a childhood study.

DR. MOTSON We have done one or two estimations on urine growth hormone but have not been able to find a satisfactory method.

DR. A. ST. J. DIXON (*Bath*) Can I ask a question for information. Is this type seen in growing children?

DR. MOTSON Yes, sleep associated growth hormone release occurs in children from 12 weeks onwards (Vigneri and D'Agata, 1971).

DR. A. ST. J. DIXON (*Bath*) And another question for elucidation. Do you feel that this is applicable to the minimizing of prednisolone damage to the collagen tissues of the body such as the bruising and the thinning of the skin and osteoporosis. Do you feel that the suppression of growth hormone is partly to blame for this?

DR. MOTSON I do not think I should go so far as to say that, since other anabolic hormones may also be suppressed by corticosteroid therapy.

DR. J. N. GLICK (*London*) Have you done any measurements on people who have had intermittent steroids?

DR. MOTSON No, but two subjects whose growth hormone was suppressed by corticosteroids had a good growth hormone rise the following night.

DR. A. ST. J. DIXON (*Bath*) What do you feel about long-acting depot preparations of steroids? I have the clinical impression that some of the worst cases of steroid damage to the tissues occur with this type of preparation.

DR. MOTSON There does appear to be a correlation between continuity of elevation of corticosteroids and suppression of growth hormone. If growth hormone suppression is associated with tissue damage, then very long-acting steroids may not be advantageous.

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A Re-examination of the Hypoglycaemia-induced 'Stress' Response of the Hypothalamo-pituitary-adrenal Axis in Patients with Rheumatoid Arthritis on Long-term Adrenocorticotrophin (ACTH) Therapy. By M. R. FLEISHER, D. N. GLASS, and J. R. DALY (*Clinical Research Division, Kennedy Institute of Rheumatology, and Department of Chemical Pathology, Charing Cross Hospital Medical School*)

There is considerable evidence that treatment with