THE DIFFERENTIAL EFFECT OF CORTISONE AND OF A.C.T.H. ON MOOD

By

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IT is evident from many reports published in the last four years that psychological changes can occur during the treatment of physical illness by Cortisone and corticotrophin (A.C.T.H.). There is no doubt, too, that similar mental symptoms have been occasioned by giving either of these agents in therapeutic doses. It is perhaps for this reason that most writers have not distinguished between them in this respect. Thus, the mild mood changes that often occur, and the relatively rare psychotic reactions are usually spoken of as complications of A.C.T.H. *or* Cortisone therapy. This implies that, in the individual case, these substances would be equivalent in their influence on the mental state; yet there are grounds for suspecting otherwise. The aetiology of these psychological reactions remains obscure, so that any evidence which serves to differentiate the psychiatric side-effects of the two drugs would be of interest.

The few writers who have explicitly considered this aspect are not in close agreement. Hench and his colleagues (1950) in an early report on the treatment of patients with rheumatoid arthritis concluded that the "euphorigenic" effect of Cortisone was greater than that of A.C.T.H. This finding has not been corroborated by later writers. Irons and his colleagues (1951) found that all of their patients with collagen disease or chronic dermatoses treated with either drug experienced a sense of wellbeing at some stage, whereas only those given A.C.T.H. exhibited abnormal mental changes; these included depressive, hypomanic and schizophrenic episodes which did not occur when Cortisone was given subsequently.

In a psychiatric study (Lidz *et al.*, 1952) of 15 patients, most of whom were asthmatics, Cortisone was thought to have less euphoriant effect than A.C.T.H. The authors could not attribute this difference entirely to the greater relief from asthmatic symptoms provided by A.C.T.H. Goolker and Schein (1953) in a detailed psychiatric report on 80 patients treated for various physical conditions were unable to gain more than an impression that A.C.T.H. is "more likely to be associated with psychic phenomena". Other psychiatric observers (Rome and Braceland, 1952; Brody, 1952; Glaser, 1953; Rees, 1953) have been, in the main, silent on this point, but occasional hints of a differential effect have been given. Clark and his colleagues (1952), for example, noted wit interest that two of their patients in whom mental symptoms occurred during or immediately after A.C.T.H. therapy, had no recurrence of this disturbance during subsequent high dosage with Cortisone. Findings of this kind, however, have so often been apparently cancelled by others of similar sequence but with the reverse order of drugs, that the lack of emphasis accorded them is not surprising.

The following report concerns a young woman with psoriasis arthropathica in whom mood variations occurred during treatment with Cortisone and A.C.T.H. Her psychological changes will be considered in relation to the effects of these agents on her physical disease and her adrenocortical function.

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CASE HISTORY

Miss P.G., aged 24.

Family History. Mother has familial tremor of hands and head. Father died when patient was aged 7: cancer of the bowel. The patient is the ninth of ten siblings: all are healthy except a brother who died aged 22 after an illness in which "his backbone turned to chalk". No other relevant physical illness or mental symptoms.

Personal History. At birth (1927) and during infancy her development was normal. She was a quiet child, who kept apart from her siblings and clung to her father. Little is known of her scholastic attainment, but at that age she was friendless and solitary.

When aged 14 she started work as a factory machinist, and had remained in her last job for 6 years, doing semi-skilled work. She lived at home with her mother and two unmarried siblings.

Menarche aged 14. Menses had been regular, 5/28, apart from amenorrhoea during chrysotherapy in 1947, and from December, 1951, until May, 1952, during a severe exacerbation of her illness. She had had only brief friendships with boys, and had shown little interest in sex or marriage.

Apart from herpes zoster at 8 years old, her physical health had been good before the onset of psoriasis.

Personality. Since early childhood she had been the "odd man out" in her family. She was taciturn and undemonstrative, with a preference for solitude and indolence. She was aloof and humourless and regarded as "moody", sullen and over-critical. She was unusual, too, in being very clean, tidy and orderly; she was quick to be angry if her belongings were moved out of place. She had no recreational interests apart from the cinema.

Present Illness—Physical. Psoriasis started in 1942 when she was 14, about 3 weeks before her first menstrual period. Until 1944 she was under the care of St. Thomas's Hospital and received topical therapy both in hospital and as an out-patient. Her scalp was never cleared, but a partial remission continued until 1947 when she suffered a severe relapse involving her face for the first time. At about this time the first symptoms of *Arthritis* began. This was confined to her feet. A course of gold injections and physiotherapy left her with only stiffness in the feet and a scaling scalp. Another psoriatic relapse occurred in 1949 without any further joint symptoms; but in the spring of 1951 she developed painful joint swellings, which were immediately followed by an exacerbation of psoriasis; this had spread to cover her entire body by December, 1951. Arthritic symptoms had subsided by then, but she was surprised to find early in the next year that movement of her shoulders was so impaired that she was unable to raise her arms above her head. Her finger and toe nails had been affected by psoriatic pitting and subungual thickening for 4 years. In spite of severe skin eruptions and painful joints she was able to remain at work until March, 1952, two weeks before she first attended the out-patient department of the Maudsley Hospital.

Present Illness—Mental. A change in her mood and behaviour was first noticed a few months before arthritic symptoms began in 1947. She became more seclusive and irritable and had brief spells of unaccountable weeping. During the next three years this tendency became more pronounced, and when either skin or joint symptoms were bad she was often manifestly depressed. In the past year depressive symptoms had seldom lifted, she was usually apathetic and morose; her irritability made her almost unapproachable. She had never expressed either suicidal or other frankly morbid ideas, but for some months she had been preoccupied with the fear of becoming a cripple.

In April and May, 1952, she was seen by Dr. Denis Leigh at the out-patient department on six occasions. Treatment consisted of brief interviews in which she was given strong encouragement and reassurance; also "mist. gent. acid." thrice daily. During this time, psoriatic lesions cleared rapidly from her face and trunk, and there was considerable improvement of her skin elsewhere. Her joint symptoms showed little change. Her affective symptoms improved appreciably. She was able to smile and talk more freely at hospital and was less gloomy and irritable at home.

On 23 July, 1952, she was admitted to the Maudsley Hospital under the care of Professor Aubrey Lewis.

On Examination—Physical. She was a tall, plump young woman of athletic habitus, with dark hair of normal feminine distribution. There was a slight diffuse enlargement of her thyroid gland but no tachycardia or other signs of thyroid dysfunction. No abnormal signs were found in the C.N.S., respiratory, alimentary or cardiovascular systems. Her blood pressure was 130/90.

Psoriasis. Gross rupioid lesions covered the scalp with some extension over the hairline. A few fresh guttate lesions were scattered over the limbs, and there was a large healing area over the sacrum. There was widespread light brown pigmentation in recently healed area on the legs, arms and face. Pitting was found on all finger nails, and all toe nails were elevated by subungual hyperkeratosis.

Arthritis. There was considerable limitation of movement with crepitus at both shoulder joints, but only slight aching in the upper arms. Both wrists and several proximal interphalangeal and metacarpophalangeal joints of the right hand were tender and swollen. Most metatarsophalangeal joints of both feet were very tender and there was reduced mobility of

several toes. X-ray showed changes which have been described (Fawcitt, J., 1950) as characteristic of psoriasis arthropathica; especially in the feet, where bone destruction with attenuation of metatarsals and joint disorganization were prominent. E.S.R. was 13 mm. in one hour (Westergren) and she had mild normocytic hypochromic anaemia.

On Examination—Mental. Her expression was set and morose; her movements were slow and constrained. She appeared to be slightly anxious, but in general her behaviour indicated apathy. There was scarcely any variation in her mood. Otherwise she showed no signs of disturbance. Her educational level was low and her intelligence was judged clinically to be low average. At this time she was relatively cheered by the recent physical improvement, but she had good insight for her previous depression. She attributed this to her arthritis and her fear of being crippled. She was less concerned by the psoriasis; when her face was not affected she had become accustomed to this. She ate and slept well and accepted hospital routine without comment.

Psychological tests. Raven's Progressive Matrices I.Q.=92; on the Minnesota Multiphasic Personality Inventory she achieved normal scores on all scales; Wechsler-Bellevue, Full Score I.Q.=89; Verbal I.Q.=77; Performance I.Q.=104 (a result in accord with her record). The clinical impression of emotional inhibition and a sense of insecurity was confirmed by her performance on the Rorschach test, to which she gave very few responses. These were also compatible with some degree of depression. The Make a Picture Story Test result suggested, in addition, that difficulties of sexual adjustment were prominent. This appeared to consist in an ambivalent attitude towards men and towards attaining full feminine maturity.

Clinical Course and Treatment. Throughout her stay in hospital she was seen every day for the purpose of observation. During the first month, while psychological and other tests were done, no special treatment was given. There was little change in her physical signs but symptoms of mild affective disturbance left her and her mood reached a level that was regarded as usual for her. From 25 July, for 6 days, she was given an inert placebo mixture four times a day orally. This was indistinguishable by taste or appearance from the Cortisone mixture given subsequently. While she was receiving placebo, physical signs were unchanged, but for a day or so she was more morose and subdued. At the time she denied feeling different, but later admitted that she had felt "depressed". On 1 August, Cortisone acetate was substituted for the placebo. She was given a total of 4762·5 mg. over 45 days. The initial dose of 100 mg. daily was gradually increased to a maximum of 150 mg. daily which she took for one week. Thereafter it was withdrawn over 17 days, and was followed by a further 15 days of placebo.

After the first few days on Cortisone there was a rapid improvement in joint symptoms. Full mobility at the shoulders was regained, muscle power became normal and she was able to walk on her toes for the first time for 5 years. At the same time psoriatic lesions steadily healed, pigmentation faded and, at the height of her improvement, apart from residual staining, her skin, including the scalp, was normal. A mood change was apparent on the first day of treatment when she spontaneously said she felt better, and was heard whistling and humming as she walked. This was followed by a few days during which she was once more gloomy and listless. In the next week her mood was variable, but by the time she was having 125 mg. daily she was consistently cheerful. By this time she was more animated, talked as much as any patient in the ward and smiled freely at interviews. She was even ashamed of her talkativeness and admitted that she tried to suppress a new tendency to giggle. While on 150 mg. daily there were times when her high spirits were immediately apparent. She giggled, grinned and joked with patients, and had a flippant, jaunty manner. She never referred to her loss of physical symptoms unless asked; then she would admit her pleasure at this. She later claimed that she had never in her life felt as happy as at this time.

When the dose was reduced, and after Cortisone was stopped on 17 September, fresh psoriatic lesions appeared on her scalp and face, and there was a slight relapse of joint pain and swelling. Meanwhile she remained steadily cheerful and contented, but the signs of euphoria had gone. A month later her scalp was as crusted as before and several joints were tender and ached. Her manner and mode of talk was again gloomy and constrained, and at times she was outspoken when annoyed, in a way she had not previously shown in hospital. By November her skin was again as it was on admission, and her joints were worse. Mentally she was little different from how she had been before treatment began.

On 21 November, 1952, inert intramuscular injections were started, preparatory to a course of A.C.T.H. These were given for 10 days. At first she was very upset by the injections; she became manifestly anxious and depressed. When the injections were transferred from the buttock to the arm she was relieved. She said she had always been distressed by injections given "behind her back". Before the placebo course finished her mood had returned to its previous level; there had been no change otherwise. A.C.T.H. was started on 1 December. This was given intramuscularly twice daily over 74 days until 6 February, 1953. She received a total of 5027·5 mg. The initial dose was 60 mg. daily; the maximum dose of 100 mg. daily was started in the 5th week and given for 17 days. A.C.T.H. was withdrawn over 3 weeks and followed by a week of placebo injections.

The physical response to A.C.T.H. was more striking than it had been to Cortisone. Her psoriasis healed more rapidly and ultimately cleared without trace. Her arthritic symptoms were completely relieved, and, apart from mild, transitory symptoms during the withdrawal

period, this remission was maintained until several weeks after treatment stopped. By contrast, signs of renewed psoriatic activity appeared as soon as the dose was reduced to 50 mg./day, and this relapse progressed until it was halted by topical therapy two months later.

During the early stages of physical improvement, her mood changed quickly, with a return of the spontaneity, friendliness and the tendency to laugh immoderately that she had shown while on Cortisone. When the dose had been raised to 75 mg./day she displayed a further elevation of mood. She said "I feel happier today than I can remember"; she remarked that she was now continually wanting to laugh. She attributed her good spirits to the loss of joint symptoms. Within two days she had lost her cheerfulness and at no time while on A.C.T.H. did her mood regain a similar high level. After a few days on 100 mg./day, by which time she had lost all physical symptoms, she complained of feeling restless and irritable. A few days later she was obviously depressed. She became solitary and inactive, and was retarded in talk and movement. She described a "fed up feeling . . . it's an awful feeling . . . I keep trying to get out of it, but it just won't move . . . I wasn't like it on the other one (Cortisone)". She was unable to recall her earlier high spirits; she said she thought she had felt more or less like this ever since the present treatment had started. There was little change in this mild depressive state for four days. For two more weeks she remained subdued and gloomy, but by the time A.C.T.H. had been reduced to 25 mg. per day she had regained her good humour, interest and activity. She was unconcerned by the return of her psoriasis: "I feel fine apart from the irritation on my head . . . I feel quite happy." But a few days later she was again mildly depressed, and this variability continued until the placebo injections stopped. Thereafter she reached an equable state of amiable contentment which continued until she left hospital on 14 April, 1953.

During both courses of treatment, there was a moderate degree of facial rounding and generalized skin bronzing; but an appreciable increase of hair growth on face, arms and legs occurred only during A.C.T.H. therapy. These changes receded within a few weeks after the drugs were stopped. Menstruation continued regularly throughout her time in hospital.

Special Investigations. Thyroid function; B.M.R. +2 per cent.; serum cholesterol 175 mg. per cent.; urinary excretion of Radio-active iodine—normal. Glucose Tolerance: a "flat" curve: E.S.R. rose to 15–20 mm. 1st hour (Westergren) before and after treatment; fell to below 10 mm. during each course.

Serum electrolytes: within normal range throughout; on maximum Cortisone dose, Na. = 317, K. = 17·2 mg. per cent.; on max. A.C.T.H. dose Na = 339, K. = 18·5 mg per cent. Blood count: there was a mild normocytic hypochromic anaemia; a moderate rise of total white cells occurred during each course.

Eosinophil count (see Fig. 1): there was a definite but irregular depression of eosinophils from a pre-treatment range of 61–169 per c.mm. to the minimum figures 15 and 10 per c.mm. on Cortisone and A.C.T.H. respectively.

17-Ketosteroids. Estimations of 24-hour urinary excretion of total 17-ketosteroids were done by the standard method recommended by the Medical Research Council (1951). There were high levels before and after treatment. When values during the four weeks immediately after each course are omitted to exclude any "rebound" effect, the non-treatment range was 12·0–40·3 mg., average = 28·9 mg. Values during Cortisone therapy were considerably lower; on maximum dosage the range was 6·4–14·3 mg., average = 10·9 mg. During the A.C.T.H. course high values were maintained and some increase of output occurred; on maximum dosage the range was 20·9–44·4 mg., average = 32·2 mg.

In view of the high 17-ketosteroid output, perirenal air studies were done at the Hammersmith Hospital; radiographs showed normal outlines of suprarenal glands. Skull X-ray showed a normal pituitary fossa. The clitoris, uterus and adnexae were found to be normal; there were no clinical signs of virilism or of abnormal fat distribution. It was concluded in consultation with Dr. Russell Fraser that there was no gross disturbance of her adrenocortical function.

Clinical Rating. For the purpose of easy comparison her clinical course was given a daily rating. Psoriasis was selected for this because it lent itself better to objective estimate than her arthritic symptoms, and because changes in the latter were less pronounced. Her skin condition was rated on a 5-point scale: 1. Normal skin; 2. Residual healing only; 3. Mild chronic and/or early fresh lesions; 4. Moderate activity; 5. Severe activity.

Similarly, a 5-point scale was used for rating Mood, thus: 1. Depressed; 2. Low-spirited; 3. "Normal"; 4. High Spirited; 5. Euphoric or elated. For this purpose euphoria was judged to be present when elevated mood was accompanied by impaired control of emotional expression, such as irrepressible giggling.

These clinical rating and 17-ketosteroid values are shown in Fig. 1 over a 38-week period extending from 2 weeks before Cortisone was started until 2 months after A.C.T.H. was stopped. The eosinophil counts are also shown.

Discussion

It may be seen that there are four general features in the relationship between the clinical course, 17-ketosteroid output and therapy as represented in Fig. 1.

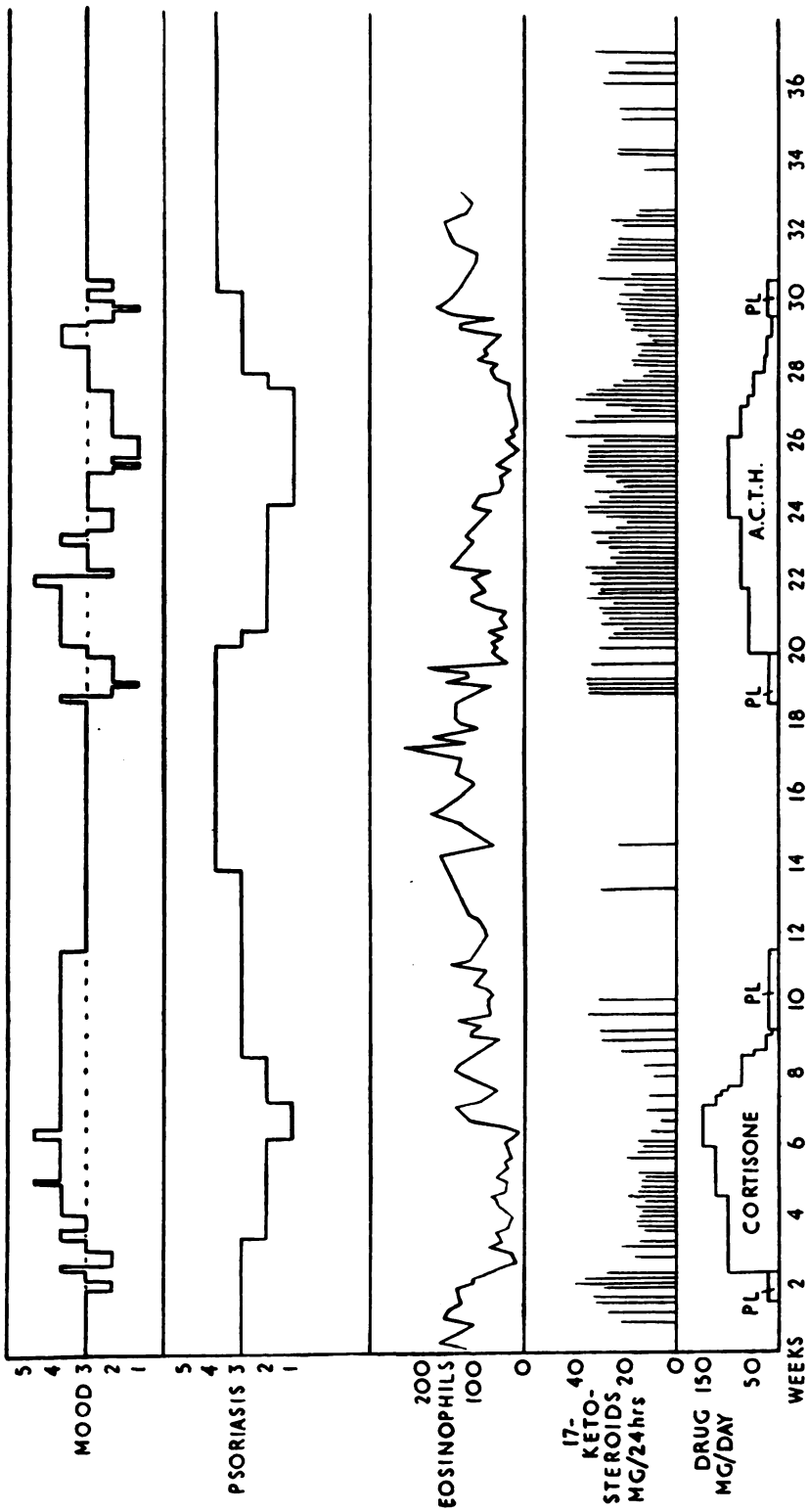

FIG. 1.—Changes in Mood, psoriasis, urinary 17-ketosteroids and direct Eosinophil Count during treatment with Cortisone and A.C.T.H.
PL = placebo.
Mood: 1 = Depressed, 2 = low-spirited, 3 = "normal", 4 = high spirited, 5 = euphoric or elated.
Psoriasis: 1 = Normal Skin, 2 = Residual healing only, 3 = mild chronic and/or early fresh lesions, 4 = moderate, 5 = severe activity.

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1. In each course of treatment, during the early stages of rapid physical (psoriatic) improvement, mood was at or usually above the normal level.

2. When higher, and particularly maximum doses were given, when psoriasis was cleared to an equivalent degree by both drugs, the corresponding mood levels were different. During the Cortisone course there was a sustained elevation, amounting at times to euphoria; during the A.C.T.H. course it remained at or below the normal level, and for some time she was manifestly depressed.

3. These opposing trends of mood are matched by the opposite effects of Cortisone and A.C.T.H. on 17-ketosteroid output. On maximum Cortisone dosage this was reduced to an average of 10·9 mg. in 24 hours, whereas at the corresponding stage of A.C.T.H. therapy the average output was as high as 32·2 mg./24 hours.

4. At times other than when her physical condition was most improved, consistent associations between 17-ketosteroid and mood levels were not apparent. For example, comparison of the findings around the 2nd, 10th, 19th and 37th weeks, shows similarly high 17-ketosteroid values at these times, but considerable differences in the corresponding levels of mood.

It is necessary at this stage to consider certain factors which might have influenced her mood at the time of greatest physical benefit from each drug. Arthritic symptoms: on A.C.T.H. she was entirely free from these; on Cortisone, although shoulder joint mobility was still slightly reduced, the patient was scarcely aware of this. Menstruation occurred at this stage during both courses. She remained on the same ward, and was given the same opportunities for activity and recreation throughout her stay. She suffered no financial loss while in hospital, and a job was kept open for her. Discussion with the patient and her relatives at the time and subsequently yielded no indication of any prominent psychogenetic factors to which the most pronounced and sustained affective changes could be attributed. Finally, there seem to be no grounds for postulating the occurrence of random and paradoxical mood swings, to which the patient was not prone.

It is now possible to interpret the findings in the following way. The patient's mental state, especially her mood, was mainly under the immediate control of three groups of factors; (i) the state of her physical disease, and particularly the rapid changes produced in this by therapy; (ii) endocrine functions reflected by 17-ketosteroid excretion; and (iii) environmental and psychological events such as those which have just been considered. The continuous interplay of all these variables would obscure the relationship between mood and any one factor. Also, any overwhelming contribution from one type of influence would alone create its characteristic effect on her mood. For example, her spell of depression in the 19th week when placebo injections were started was clearly related to her dislike of intramuscular injections: similarly the rapid improvement in physical symptoms in the early stages of both Cortisone and A.C.T.H. courses was associated with elevated mood. It remains, then, to observe the effect of bringing certain of these factors "under control". For this purpose, suitable conditions obtained when she was receiving high doses of both drugs. At these times, as far as it is possible to judge in an ordinary clinical setting, environmental and other contingent factors were equivalent. In each instance her physical disease was under fullest control and she was free from symptoms. It is, therefore justifiable to examine the relationship at these times between mood and the remaining variable; that is, 17-ketosteroid values.

Under these circumstances, the associations of reduced 17-ketosteroids with elevated mood, and of raised 17-ketosteroids with depressed mood assume significance.

It is interesting to note that the mood changes in this patient were relatively mild. They were, in fact, of a degree and quality which could easily have encouraged the view that they were due to other factors: one might have postulated either pleasure at symptom-relief, or, by contrast, an unacknowledged reluctance to lose the benefits of illness. Yet there can be little doubt that the 17-ketosteroid changes, which related to her mood variation, were produced by the action of the drugs on her adrenal cortex. The suppressive action of Cortisone was probably due to its inhibitory effect on pituitary–A.C.T.H. release (Sayers, G. and Sayers, M. A., 1948; Lewis *et al.*, 1950); although the possibility of a direct action on the adrenal cortex does not seem to have been ruled out. It follows, therefore, that mood changes occurred which were directly attributable to exogenous Cortisone and A.C.T.H.; and, in this patient, the effects of these drugs in this respect were different.

How may these findings be explained and at the same time reconciled with the lack of consistent psychological response to these drugs which is so evident from previous reports? It could be, simply, that this patient's mood was influenced by the absolute levels of circulating androgens, from which the greater part of urinary 17-ketosteroids is thought to derive; so that Cortisone elevated her mood by reducing androgen secretion, whereas A.C.T.H. produced the reverse effect by accentuating one of the endocrine components of her depressive disposition. It might be argued, also, that a similar relationship between mood and 17-ketosteroids has not been found generally in patients under treatment, because most of these begin with low rather than high 17-ketosteroids; hence this patient was unusual in a significant respect. This explanation, however, throws no light on the general problem; furthermore it takes no account of the increase of Cortisone or Cortisone-like activity which must have occurred during both courses of treatment. In the first this was due to oral dosage with Cortisone, in the second it was provoked by A.C.T.H. When this factor is considered, it suggests that mood may have been influenced, not by absolute levels of individual adrenocortical products, but by changes in the relative proportions of circulating androgens and Cortisone or its equivalent. The exact ratio of these is not known in this case, because only 17-ketosteroids were estimated, but there is some warrant for the view that a disproportion of this kind may be associated with mental changes.

Hoagland and his colleagues (1953) found that "schizophrenic patients showed lower than normal rates of excretion of corticoids and phosphates, and thus displayed at rest evidence of both hyperadrenalism and hypoadrenalism". Rowntree and Kay (1952), who made detailed observations of two patients with recurrent schizophrenic episodes, found evidence of "a dissociation between different adrenocortical steroids, the various stages of an attack being associated with a relative preponderance of different steroid fractions". At the height of an attack there was a preponderance of androgenic substances. Reiss and his colleagues (1949) report a case which is of particular interest in this connection. Their patient had alternating phases of mania and depression. They found an inverse relationship between beta-ketosteroid and low cortin excretion; during the transition to mania beta-ketosteroids fell and cortin excretion rose. It is possible that a similar disproportion, or even an inverse relationship of this kind accompanied the mood changes of the patient reported here. It is evident that "the point at issue is not entirely whether the adrenal gland is

hyperfunctioning or hypofunctioning. Qualitative rather than quantitative changes in adrenocortical output may be the key to understanding the relationship between the endocrine system and mental illness" (Cohn *et al.*, 1954).

Regarded in this light it is not surprising that characteristic differences between the psychological effects of giving Cortisone and A.C.T.H. have not been demonstrated. If these effects depend on a disproportion such as between androgens and corticosteroids, either drug may produce them. Whether there is a specific association between the type of disproportion and the quality or incidence of mental changes can only be discovered by serial observations in many cases. In any event it is probable that these reactions are at least partly determined by the functional state of the adrenals before the drugs are given.

The search for significant correlates of the mental symptoms occasioned by A.C.T.H. and Cortisone therapy has not, so far, been fruitful. Individual susceptibility to them does not appear to be related to either the response to previous courses of treatment (Clark *et al.*, 1953) or previous mental disorder or emotional instability (Lewis and Fleminger, 1954). It is doubtful whether the psychological mechanisms which have been postulated in some instances are more generally applicable than the electrolytic disturbances that have been reported (Ransohoff, W., 1951). It is likely that a complex of factors is concerned. Among these, the modification of adrenocortical function induced by these drugs is probably always contributory, and, given suitable conditions, may sometimes be crucial.

Summary

An account is given of the response to treatment with Cortisone and A.C.T.H. of a young woman with psoriasis arthropathica.

The relationship between changes in her mood, physical symptoms and urinary 17-ketosteroid values, indicates that mood variations occurred, which were directly attributable to the drugs, rather than to symptom-relief or other factors.

Cortisone led to an elevation of mood; A.C.T.H. provoked depressive symptoms.

It is suggested that Cortisone and A.C.T.H. may have influenced mood by producing changes in the relative proportions of androgens and other adrenocortical products.

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