

TOXIC PSYCHOSIS UNDER CORTISONE AND CORTICOTROPHIN

By

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It is generally conceded that the majority of effectual therapeutic remedies carry potential hazards, some of them incalculable.

In the case of Cortisone or Corticotrophin (A.C.T.H.), the passage of time since these were first employed in 1950 has permitted an appraisal of their associated risks.

The object of this paper is to stress the undesirable mental reactions from these hormones, now in wider use, and to illustrate the pattern of such complications from three case-histories in my personal experience.

THE RISKS

The major risks are of two main orders, namely, the suicidal depressives (Pearson and Eliel, 1950; Borman *et al.*, 1951; Galdston *et al.*, 1951; Kirsner and Palmer, 1954), and those seriously disturbed who have been submitted to prefrontal leucotomy (Hellier, 1954), due in one recorded instance to hypomania (MRC Panel, 1954).

Between these two extremes any degree of mental reaction may occur.

INCIDENCE

Changes in mood are more commonly noted than major mental disturbances, as is evident by reference to Table I.

The amelioration of physical symptoms with resultant euphoria or mood-enhancement provides a psychological reaction in keeping with the natural response to treatment, and offering comparison with varying grades of depression when the patient's expectations from the "wonder drug" are tardily rewarded.

The incidence of psychotic reactions is admittedly low, namely 4 per cent. (Table I), but Ragan (1953) quotes an overall figure of 36 per cent. for mental symptoms, noting that in his series these reactions were all reversible although the severer grades required electroplexy for their termination.

PREDISPOSITION

This term implies an innate constitutional susceptibility distinct from predisposing factors, which may be classified as endogenous (age and sex) or exogenous (drug-dosage, treatment-duration and physical disease).

Constitutional susceptibility is inferred from the pre-morbid personality or previous history of mental breakdown or similar family-history, but Professor Aubrey Lewis and Fleminger (1954) have shown that even a positive past-history of psychotic breakdown does not confer any special vulnerability to Cortisone.

Ward *et al.* (1951) reported a higher incidence of mental reactions in women particularly in the menopausal age-group, but in their series of five women aged between forty-six and sixty-nine with rheumatoid arthritis treated from twelve

TABLE I
Summary of Published Series with Mental Reactions Under Cortisone or Corticotrophin

Author	Year	Drug	Total No. of Cases	Disease Indications	Duration of Treatment	Affective-State		Psychosis	Outcome
						Eu-phoria mania	Depres-sion Stupor		
1 Boland, E. W.	.. 1951	C	76	Rheumatoid Arthritis	6-15 months	2(*)			
2 Ward, E., et al.	.. 1951	C	100	Rheumatoid Arthritis	Long-term	29(*)			
3 Lidz, T., et al.	.. 1952	A & C	15	Various but in 10 cases Asthma	8-38 days	4	2	2	
4 Glaser, G. H.	.. 1953	A & C	200	Various	13-155 days		1	10(t)	E.C.T. in 5
5 Levin, M. H., et al.	.. 1953	A & C	50	Arthritis	18 months			5(z)	
6 Taran, L. M., et al.	.. 1953	A & C	16	Rheumatoid Carditis	Long-term	6(y)	3		
7 Copeman, W. S., et al.	.. 1954	C	20	Rheumatoid Arthritis	Long-term		1		
8 Engleman, E., et al.	.. 1954	C	56	Rheumatoid Arthritis	4-38 months	9(x)			
9 Kirsner, J., et al.	.. 1954	A	120	Ulcerated Colitis	1-4 years	23	13	8	Suicides in 2
10 McGehee, E. H., et al.	.. 1954	A & C	185	Various	Long-term			3	Leucotomy in 1
11 MRC Panel	.. 1954	A & C	124	Skin Disorders	Short-term	2	1	2?	
12 Tretthowan, W.	.. 1954	A & C	17	Rheumatoid Arthritis	?			3	
13 Bunim, J. J., et al.	.. 1955	A & C	78	Rheumatoid Arthritis	Up to 4 years		4		
14 Fox, H. M., et al.	.. 1955	A & C	100	Various	? months			16	
15 Pearson, J. E. G.	.. 1955	A	10	Asthma	Short-term	1			
16 Toone, E. C., et al.	.. 1955	C	35	Rheumatoid Arthritis	Up to 3 years		1	1	1

(*) Described as "mental stimulation" and "nervousness".

(x) Described as "emotional instability".

(t) Includes 2 "manic", 1 manic-depressive, 4 organic (paranoid-depressive), 2 organic (paranoid), and 1 organic (depressive).

(y) Associated with other complications, e.g. Cushing's Syndrome.

(z) Includes 3 manic-depressives and 2 paranoid-schizophrenic reaction-types.

A Refers to A.C.T.H.

C Refers to Cortisone.

to twenty-four months with Corticotrophin (A.C.T.H.) at Sheffield, West and Newns (1955) encountered no mental reactions.

The role of pre-morbid personality-structure has received considerable emphasis by some authors. For example, Copeman (1954) refers to psychosis as the most serious complication of hormone treatment and regards present or past psychosis an absolute contra-indication to such treatment.

Dunlop (1955) finds that Cortisone exaggerates neurotic, psychotic or epileptic tendencies, and should be employed only for very compelling reasons in those with an unstable mental background. Professor Wayne (1955) of Glasgow prefers not to treat a patient with a history of mental disturbance, but adds that it is by no means certain that any ill would result.

On the other hand, none of the ten cases with minor or major mental reactions listed by Clark *et al.* (1952) gave a history of previous mental breakdown, from which these authors conclude that the basis of individual susceptibility to these hormones remains an unknown quantity.

Glaser (1953) is of the opinion that the pre-morbid personality determines the psychological content of the psychosis but not its onset.

Aubrey Lewis and Fleminger (1954) point out that the unknown factor predisposing to a mental reaction under Cortisone can hardly be derived from the corresponding hereditary or environmental constellation ending such cases with an antecedent mental breakdown unrelated to Cortisone therapy; also, that a predisposition to the occurrence of mental illness is distinct from the form such illness may take.

With regard to dosage and duration of treatment, it is known that the risks of mental reactions are in direct ratio to high dosage or prolonged courses of treatment; similarly, too rapid reduction of hormone towards the conclusion of a course may lead to "withdrawal symptoms" with conspicuous depression. Nevertheless, Clark (1952) and Glaser (1953) could find no consistent correlation between drug-dosage and the onset, duration or type of psychotic reaction.

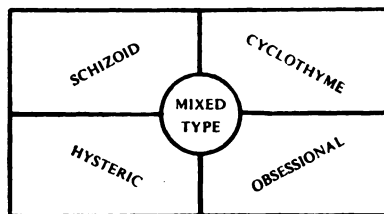
From various trials the tentative impression emerges that the collagen diseases (Wayne, 1955) and Addison's disease of the adrenal glands render their subjects more vulnerable to mental disturbances than other physical diseases, although in the main the complications of Cortisone or Corticotrophin are similar for the great majority of conditions for which these hormones are utilized (Duthie, 1955).

The influence of the various determinants is reflected in Table II.

THE CLINICAL PICTURE

(a) *Mode of Onset*

The major psychotic disturbances are heralded by premonitory subjective and objective deviations of mood with accompanying vague somatic symptoms before behaviour or thought-processes become manifestly disturbed. The type of mood-change depends upon the basic personality-structure of the individual as outlined on the following schema:



In mixed types of personality, for example one occupying the central circle rather than an independent square, the mood-change would be modified. Somatic symptoms are more frequent in the hysteric, are referable to any system but may occur more frequently as indescribable "painless" headaches, vague shifting paraesthesiae and undue transient visceral awareness without localization.

(b) *Course*

Of the psychotic-like reactions, Glaser (1953) notes two major patterns, namely (i) primarily affective disorder either manic or depressive, and more frequently (ii) an organic reaction (toxic psychosis) with associated paranoid-hallucinatory and/or affective (usually depressive) components. Fox *et al.* (1955) describe the mental reactions as the result of the inter-play of the following three factors on the patient's personality, namely (i) the pharmacological effect of Cortisone or Corticotrophin on the total personality; (ii) the meaning to the patient of the alteration in the symptoms of his disease; (iii) the nature of the patient's fantasies about the action of the administered substance ("wonder drug"). These authors found disturbances of mood, of thinking and of the perception of reality with minimal or no clouding of consciousness, no disorientation nor intellectual deficit.

Clark, Bauer and Cobb (1952) were impressed by the invariability of disturbances of speech and affective disorder, while delusions, disturbances of body-image, motor disturbances and depersonalization were inconstant features in their series of psychotic reactions. These authors noted that the psychotic features due to Cortisone presented a fragmentary structureless picture in unpredictable sequence without the disorientation and sensorial disturbance characteristic of a toxi-delirious state.

Professor Anderson of Manchester University (1955) remarks that the protean character of the symptomatology of psychosis following Cortisone has been a feature of the condition, and describes the occurrence of both depressive and manic phases in one case with paranoid trends in a setting of mild clouding of consciousness—a combination of syndromes somewhat distinctive.

(c) *Outcome*

Exceptionally, they may respond dramatically, but by and large the cortisone-precipitated psychotic reactions revert progressively (*vide* Table II for duration of the mental symptoms) once the offending hormone is discontinued or the dose drastically reduced, but recovery is not invariable and the risk of suicide very real.

In so far as rheumatoid arthritis, ulcerative colitis, asthma and certain skin disorders often are psychogenically determined, the effect of the patient's attitude to his physical disease is no less important than the influence of a potent hormone on his basic personality-structure.

CASE HISTORIES

Case 1

J.F., male, aet. 64, of pyknic build, with a history of ulcerative colitis for thirty-three years dating from 1919 following various traumatic incidents in the Great War including "gassing" for which he drew a disability pension. He had suffered innumerable exacerbations of his symptoms having a temporal relationship to changes in residence, in his occupations, and the vicissitudes of family affairs until admitted for treatment with Cortisone at a dosage of 100 mg. daily. A course lasting six weeks was completed uneventfully, but the effect was short-lived and some two months later he was readmitted for a second course.

During the first week, it was obvious he was extremely low-spirited, he did not smile, nothing interested him; he was attuned to a morbid introspective hypochondriacal pre-occupation that even the "wonder drug" could not cure him—all these features occurred in a markedly depressive setting without clouding of consciousness.

For the next five days his prevailing mood of apathetic depression fluctuated little if at all; he was harassed by insomnia, anorexia and diarrhoea, and reiterated the wish to be "back at the front in the War". He maintained a hostile, resentful attitude towards the staff, regarding food and medicines alike with disdain if not actual refusal.

In the course of a week, Cortisone resulted in a reduction of the bowel-frequency and the disappearance of sanguineous motions; the patient was aware of this, which coincided with a dramatic lifting of his depression, which had lasted in all about ten days.

Unfortunately, his subsequent course was marred by the development of jaundice and enlargement of the liver, which was firm, nodular and tender; he failed to recover, and autopsy disclosed metastases in the liver and polyposis of the colon with histologically demonstrable malignant change. This case has been reported elsewhere (Truelove and Witts, 1955). Intracranial metastases were unidentified histologically.

Case 2

M.S., married woman, aet. 28, leptosomatic in build, below average intelligence and of insecure dependent personality, had been subject to "fits" in infancy, but her adolescence was uneventful until the age of eighteen when three consecutive emotionally-laden events in her life ushered in bouts of diarrhoea, which four years later was diagnosed as ulcerative colitis: firstly, the sudden demise of her maternal grandmother ("clot in the brain") who had brought her up and whom she regarded as her mother; also the sudden loss of her father—both events witnessed by the patient with profound grief-reaction; finally, her rejection by her lover "after the banns had been called".

A year later she met her present husband, but even then she used to spend hours daily at the Cemetery. Her marriage in 1952 to an erratic, vagrant individual was not a happy choice for economic reasons, as jobless periods provoked symptomatic exacerbations of her diarrhoea as much as a miscarriage did in 1953, and the husband's eventual engagement in the Regular Army as an insurance against unemployment was a mixed blessing, for postings abroad extended her illness.

No permanent benefit having accrued from usual methods of treatment, she was given (i) A.C.T.H. 30 units twice daily from 7 till the 12 December; and (ii) Cortisone 50 mg. twice daily from 13 to 20 December, 1954.

On 28th she was a trifle elated and showed a degree of impairment of self-identification in that she referred to herself as "Doris" (not in fact one of her eight first names!), and left her relatives with the impression of being "odd" by calling one of her aunts "Bovril" (worked at this factory) and another aunt "Red Jumper".

The next day she was tearful, perplexed and evinced a greater degree of affective response than the circumstances warranted; for example, when asked why she was crying, she replied that she had not received a christmas card from her husband in Korea.

On the 31 December her mood, thought-processes, and behaviour became bizarre: she shouted out the names of her physicians at intervals, evidently in response to hallucinations; she approached her relatives with a Bible in her hand, demanding "my mother is dead—isn't she?"; she insisted that the electric light in her bedroom must remain switched on even in daylight, rationalizing that she was afraid of the dark.

On 1 January, 1955, she was tending to lose reality-contact with her surroundings, and now frankly accused her physicians of murdering her. The next day she became hypomanic and required sedation before admission to hospital effected on the following day, when she appeared dazed, was apprehensive of the dark, and was hallucinating manifestly both auditorily and visually, in response to which she would posture with clasped hands gazing towards a corner of the ceiling in an attitude of meditation, regardless of questions put to her. She whispered rather than spoke: she did not know whether she were in a hotel, school or hospital; she asked to see a former physician by name but could not define her reasons; she could not recall the names of the staff she saw daily; these features were present in a setting of mild clouding of consciousness, continuing for the next eight days. Physically, she was anaemic, undernourished and showed glossitis.

In view of her refusal to take nourishment, electroplexy was given on two consecutive days followed by feeding, after which her negativistic attitude commenced to change.

On 10 January, her sensorium had not yet cleared: she asked if she might "spit on the spittoon 'cos I can't spit on my tongue". Four days later, she smiled for the first time and appeared to appreciate the point of remarks made to her. On 20 January, she recognized us by name, and endeavoured to engage in occupational therapy, but was somewhat solitary in her habits and fond of day-dreaming. Her physical symptoms fluctuated but there was a sustained response to anti-anaemic measures.

In the interim, her husband had been recalled from Korea, but this step did not result in any dramatic improvement; as late as 4 February, during the visit of the Mass Miniature Radiography Unit she expressed the fear that "she was to be put on the trolley to be taken to the fire". At the time she could not account for these thoughts, but a week later confessed that "they were silly".

From this stage she made an uninterrupted recovery as regards her psychosis, but her mood was one of resignation to her physical illness without undue embarrassment, and she was discharged from hospital on 5 April, 1955—the total period of her mental illness lasting forty-two days.

Case 3

L.P., widow, leptosomatic in build, aet. 49, of stable personality, whose climacteric was sudden in onset three years previously following the demise of her invalid husband with rectal neoplasm in the course of a month. One of the patient's brothers had spent an indefinite period at a mental hospital. For twenty months, she had been under treatment for rheumatoid arthritis and finally was given a trial of A.C.T.H. from 22 to 28 October at 25 units six-hourly; and from 29 October to 1 November 25 units twice daily, when the course was suspended (11 days in all) in view of her mental symptoms.

On 28 October, vague band-like pains in the head oppressed the patient, followed by paraesthesiae in the digits the next day; on 30th, she was elated in mood, showed inconsistent levity at Divine Service during which she alleged the hospital ward was transformed into a beautiful cathedral with timbered naves, where the congregation consisted of the patients in white "like angels"; as she left the ward, she asserted she was informed by other patients that "the wrong man took the Service"—implying that it should have been the Bishop instead of the usual minister to the Hospital.

On 31 October, when beds were being prepared in the evening by the nurses, she felt that "they were getting at me with white sheets as if I were to be put in a coffin". That night she believed she were back in her 'teens and in a palace, and told the nurse "I have seen God and He has convinced me I can do all this . . .". On the morning of 1 November, there was mild clouding of consciousness which appeared to clear that evening when she tried to recall unsuccessfully the happenings of the day and the names of the visiting doctors whom she saw daily. During the night she was hallucinated cutaneously, protesting that her pyjamas were soaking wet, but the lability of her mood was evident by her ready acceptance of the nurse's reassurance, without affective discharge.

On 2 November, she was compulsively motivated to stoking the fire and pulling the toilet-chain, regarding these activities as devices whereby "I can make myself clean"; in mood she was mildly agitated. On 3 November, she was elated and remarked she was on the stage with her entire family including her parents (both in fact deceased), and they exchanged greetings with her. She continued "I was happy, and I got up and sang for them:

'Around the throne of Heaven a lot of children stand,
Children whose sins are forgiven in a happy land'";

during this interlude she alleged the "sun shone only to my right", but she could not elaborate on the meaning or physical aspects of this phenomenon. The next day she was hallucinating visually, describing herself as being influenced by a beam of light which coursed round the room trying to find somebody till it picked on her; momentarily, she was "like Christ". She continued "then wonderful colours of a queen came over me which I did not want, but I was surrounded by bishops and surgeons".

On 5 November at night, she experienced the sensation of gentle levitation of the entire bed "as if carried on air"—which she ascribed to the effects of a supernatural Power endeavouring to use her as an "agent to prosper the world and people in it". The next day she was hallucinating visually, with posturing; when questioned, she replied she was conversing with God Whom she could see.

Three days later, she appeared to have regained reality-contact with her environment and to have insight. Her physical symptoms had been relieved, and the total period of her mental symptoms was ten days.

COMMENT

The three cases herein recorded present such different pictures that to find unity among diversity appears at first sight unlikely.

Cases 1 and 2 have in common their physical condition, their stable family-histories, sustained exposure to a variety of stressful situations, and their similar personality pattern; they differ in the temporal sequence of their mental reactions to hormonal treatment and in the pattern and duration of this reaction. Continuation of treatment in Case 1 met with as good a response as Cleghorn and Pattee's (1954) second case in whom the dose was actually increased despite mental symptoms.

Cases 2 and 3 resemble each other in their alternating depressive and hypomanic features, with paranoid trends colouring the picture at a depressive end of the scale; and in their mild clouding of consciousness during the early

stages of treatment. They differ in age, physical disease and in duration of the psychotic reaction.

It would appear to be a fair commentary that psychosis can be precipitated by Cortisone or by A.C.T.H., but is neither predictable nor reversible in any given case. In some, suicide has eventuated, in others psycho-surgical measures, i.e. leucotomy, have been employed. Certain diseases such as Addison's and the collagen diseases render their subjects unduly susceptible to side-reactions of a psychiatric nature, in particular if these are women of menopausal age, who form the large bulk of those under treatment for rheumatoid arthritis and may constitute one group of cases of ulcerative colitis of late onset (Banks and Klayman, 1953).

Premonitory symptoms of mood-change in either polar direction of depression or elation signify more serious disorder and should be anticipated at any stage of treatment with the hormones; if present, continuation of treatment requires a nice judgment balanced against a background of possible psychiatric illness whose outcome may be the major and avoidable hazard.

Hoefler and Glaser (1950) consider that the mental changes represent the release of a psychotic reaction through the exaggeration of pre-morbid personality trends or the occurrence of an organic mental reaction—or the interplay of both factors.

Rome and Braceland (1952) suggest that the sudden and profound variation in the "milieu intérieur" by the hormone disrupts the patient's psychological adaptation consisting of the organization of his personality, the psychological meaning of the disease to him, the emotional investment in his physical person and the significance of the secondary gains.

It may be that Fox, Gifford and Murawski (1955) are nearer the truth when they point out that on theoretical grounds, every individual may be capable of reaching a threshold of tolerance to Cortisone or A.C.T.H. under a given dose for a certain period—beyond which metabolic or psychological equilibrium becomes so strained as to impair the individual's capacity for physiological homeostasis on the one hand and for the maintenance of emotional balance on the other.

In accordance with this view, the administration of these hormones constitutes an additional non-specific stress to which the organism is unable to adjust because its "psychological emergency reserve" has been exhausted through existing physical disease and its emotional accompaniments.

As a footnote it may be added that A.C.T.H. and Cortisone have been used experimentally in two series of cases by Glaser and Hoch (1951) and by Rees and King (1952) in the treatment of schizophrenia; in the first group of six cases, a woman of twenty-three displayed striking psychic changes resembling the type of psychotic reaction induced by A.C.T.H., while in the second series temporary exacerbation under Cortisone was corrected by cessation of the drug.

SUMMARY

1. Psychotic reactions may be induced by Cortisone or by A.C.T.H., in the course of which suicidal depression or serious mental disturbance requiring leucotomy may add to the known physical risks of treatment with these hormones.
2. No constant feature of premorbid personality has been determined that may guide clinically in the anticipation of the more serious grades of mental reaction.
3. Women of menopausal age appear to be more susceptible to these reactions.
4. There is no correlation between electrolyte imbalance and the development of mental reactions.

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