INVOLUTIONAL MELANCHOLIA.

A STUDY OF TWENTY CASES TREATED WITH THEELIN.

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IN the treatment of involutional melancholia the administration of oestrogenic substances has for years been a feature. The results achieved with this form of therapy have varied, some workers claiming unqualified success, and others recording no change, or even deterioration in their patients.

Werner, Kohler, Ault and Hoctor, in 1936, treated 21 patients with theelin over a period of six months and claimed 13 to be markedly improved (1). Using oestradiol benzoate, Jones, MacGregor and Todd treated 17 cases and found that six recovered with an average stay in hospital of three months (2). Schube and his colleagues treated ten cases with theelin, and not only obtained negative results in all cases, but also found three patients to be worse both mentally and physically (3). Ault, Hoctor and Werner, in 1937, treated a further 14 cases and were emboldened to state, " For all practical purposes theelin seems to be a specific in involution melancholia " (4). Again on the debit side Notkin, Dennes, and Huddart treated 15 cases, and at the end of treatment stated that three patients could still be considered somewhat improved, whilst two others were showing signs of improvement. Improvement in all cases was purely institutional, no patient being sufficiently well to resume life outside, and furthermore, at a recheck three years afterwards the entire group was found to have relapsed (5). Nevertheless, Ault in 1940 (6) was claiming a recovery-rate of over 90 per cent. in uncomplicated involutional melancholia, although he now recommended the employment of a much larger dosage.

Wittson, in a series of cases with a total dosage varying from 72,000 to 500,000 international units, over a period of 3 to 13 months recorded the following results: Recovered, 8·7 per cent.; improved and paroled, 21·7 per cent.; improved, but not sufficiently for parole, 8·7 per cent.; unimproved, 60·9 per cent. (7). He criticized the results claimed by Werner, Ault and colleagues, and pointed out that the high recovery-rate was obtained by eliminating from the series those patients who failed to respond to theelin. Moreover, since a history of previous mental illness in their cases did not exclude the diagnosis of involutional melancholia, he wondered how many of their recoveries were manic-depressives.

During the past two years considerable work on the endocrine treatment of this psychosis has been carried out, in this country more particularly by Hemphill and Reiss (20, 21).

In the present series 20 cases were examined, the material being accumulated from the hospital population after the elimination of those where the symptomatology indicated an additional element of a paraphrenic, manic-depressive, or organic nature. Furthermore, patients over 60 years of age were regarded as less profitable subjects for investigation and treatment, and were left out of consideration. All the cases presented depression without retardation, anxiety, and the typical trends or delusions. The average individual dose of theelin was 10,000 units, whilst in the most resistive cases so large a dose as 100,000 units was employed in view of Ault's claim for the efficacy of heavy dosage. Of the total dosage the minimum employed was 32,000 units and the maximum 2,100,000. The minimum length of treatment was one month, the maximum six, and the average duration two months.

In order better to assess the response to treatment, investigation was made into some factors bearing on the psychosis.

Influence of Heredity and Environment.

Twelve out of the 20 were found to have abnormal heredity in the direct, collateral, or atavistic line. Involutional melancholia, schizophrenia, neurasthenia and mental deficiency were encountered. Direct inheritance occurred in six cases, and of these mother-daughter transmission was apparent in four, whilst in a fifth both mother and father could be implicated.

With regard to environmental influences the usual finding of a greater rural incidence in involutional melancholia was confirmed in the present series. Twelve cases came from the rural areas and eight from the towns. There appeared to be an increased tendency towards recovery in the rural group, eight out of twelve, compared with the urban, four out of eight, and the average duration of the illness in the former group was considerably less than in the latter, 3·8 years compared with 5·1. Moreover, the average age at the commencement of the psychosis was 44·3 years in the rural series compared with 42·7 in the urban. Lest this should be a coincidence, all discharges of female involutional melancholics for the preceding three years were scrutinized. Although the higher rural recovery-rate was not substantiated, the other findings appeared to be borne out, for in the rural group the average duration was 1·15 years, and in the urban 1·5, whilst the average at onset in the rural was 45·6 years compared with 42·4 in the urban group.

Unless a purely regional factor is operative it seems not impossible that patients predisposed to involutional melancholia may have encountered greater adversity in the more intricate society of an urban environment, and thus developed their psychosis at an earlier age than they would have done in purely rural surroundings.

Prepsychotic Personality and Physical Type.

The prepsychotic personality in those people who develop involutional melancholia has been studied by various investigators.

Palmer and Sherman examined 50 cases from this aspect, and found constantly a definite reaction type wherein were featured marked introversion, sexual maladjustments, strong obsessional character, and hyper-religious trends (8). From a study of 80 cases Wittson found that a strong predisposition to involutional melancholia existed in the personalities of those women who developed the psychosis. He found the predominant characteristics to be quietness, sensitiveness, anxiety, over-conscientiousness, inability to confide in others, submissiveness, and sometimes stubbornness and jealousy (9). The present cases were in essential agreement with those last described. A tendency to be easily worried was prominent throughout, as were also such features as restricted interest, sensitiveness, reserve, marked conscientiousness, lack of sociability and timidity. A hyper-religious trend was noticeable only in one case.

The physical type met with was predominantly asthenic, 60 per cent., whilst pyknic comprised 25 per cent., and dysplastic 15 per cent. Bearing in mind the greater diversity of racial types in the United States, these percentages may be compared with the figures obtained at the Central Islip State Hospital, where from the investigations of 272 cases the findings were asthenic 43 per cent., pyknic, 37 per cent., and dysplastic-athletic 20 per cent. (10).

Relation to Menopause and Marital Status.

It has been pointed out that in a certain proportion of involutional melancholics the involutional period itself appears to be the most important factor in the aetiology (11), and the importance of this period as a time when anxiety normally mounts has been indicated (12). McCurdy, however, has given it as his opinion that physical change during involution cannot be the only factor (13), and this would seem to be borne out in the patients now under consideration. In all of the twelve cases where the psychosis coincided with the menopause other factors were present and the menopause was the last of a series.

Examination of marital status enabled four groups to be established—single, married and childless, married and with family, and widowed. Eight patients

were single, four married and childless, seven married and with children, and one widowed. In the case of the single patients the love interest had not been entirely absent; two had had prospects of marriage, and the loss of these was probably contributory to their illness, whilst the promiscuity of a third seemed reflected in her delusions of sin. Of the four childless married patients three were poorly adjusted and marriage had occurred later in life. Of the seven married women with one or more children, six were happily married.

When the age at onset of illness and the duration of the psychosis at the commencement of treatment were compared in these groups, the following facts emerged:—Average age at onset and average duration at beginning of treatment: Single, 43·8 and 4·8 years; married and childless, 38 and 5·8 years; married and with family, 45·5 and 1·9 years. The single women in the series would appear to give some support to Stoddart's views on the "evil influence of a single life" (14), but on the other hand the pernicious effect of an unhappy marriage could be deduced even more. Of the third group five have left hospital as recovered. This is in keeping with the investigations of Palmer and Sherman in their 50 cases, where they found that all patients who had children and whose relation to them was good were in the group that recovered. They concluded that normal family life had a definite influence in diminishing the malignancy of the psychosis.

Other Predisposing and Precipitating Factors.

Psychic factors were prominent in most, and included financial worries and worry over future security, illness and death of relatives, unsatisfying or unhappy marriage, unsatisfactory childhood environment, and effects of war as manifested in air-raids and calling up or loss of relatives. Adverse childhood played a part in six cases, but in five of these abnormal heredity was also implicated. The effects of war were evident in seven cases and in three provided the final factor. In three other cases the precipitating factor was operative interference—ovariectomy, cholecystectomy, and operation on foot. One case developed subsequent to influenza.

It is noteworthy that of the five patients who responded most quickly and most satisfactorily to theelin there were fewer factors involved, in none of them was there an unhappy childhood, and in only one was heredity implicated. On the other hand, of the four who failed to respond there were adverse childhood conditions in three, abnormal heredity in three, late childbirth in two, severe physical disability in one, and additional psychic factors in all. Moreover the average duration of psychosis was two years in the first group compared with four in the second, prior to the commencement of treatment.

Investigation into the history of these patients revealed, then, that not one, but several factors, physical and psychic, contributed to the onset of their illness. Furthermore, those cases where factors such as abnormal heredity and adverse childhood were present, and where marked psychic trauma could be postulated, were those wherein the psychosis was severest and most resistant to treatment. Conversely, those cases where the menopause was partly causal and where other factors were less prominent tended to be of shorter duration and more responsive to treatment.

Endocrine Types.

From the endocrinological aspect three types could be discerned: those where no upset other than that characteristic of the menopause was present; those where hyperthyroidism was present in addition to ovarian dysfunction; and a group of pluriglandular insufficiency. The first group, by far the largest, was characterized by increase of fat in the typical ovarian sites and by vasomotor instability. Included here were those patients who were past the acute phase of glandular change and who did not show signs implicating glands other than the ovaries. A case of artificial menopause belonged to this group, and the initial severity of her psychosis was probably conditioned by operative interference (15).

Those in the second group, two in number, presented the usual signs of mild hyperthyroid activity, such as tremors, profuse perspiration, von Graefe's sign, marked vasomotor instability with tachycardia and extra-systoles, tendency to subfebrile temperatures, and increased basal metabolism.

In the third group, that of pluriglandular insufficiency, two cases were hypothyroid and the third hypo-adrenal. The two former corresponded to Zondek's thyro-ovarian insufficiency (16), and were characterized by dryness and roughness of skin, dry, scanty and brittle hair, diminished perspiration, sensitiveness to cold, bradycardia, and a certain slowness of movement. Basal metabolic rate was reduced in both. The case of hypo-adrenia was lean, with a poorly developed musculature, and marked debility and fatigability. Considerable weight had been lost. Anorexia and gaseous distension were marked on admission and the skin was pigmented a light brownish shade, particularly noticeable on the face. The pulse was of diminished volume and blood pressure slightly reduced. The picture was in keeping with the mild and comparatively benign form of the syndrome to which the term "Addisonism" has been applied (17).

Effects of Treatment.

It became evident in the course of treatment that, depending on the response, there were four types of patient, namely those showing (1) pronounced improvement, (2) slight improvement, (3) no improvement, and (4) deterioration.

There were five patients where the effect of theelin therapy was pronounced, and where the oestrogen could reasonably be regarded as an important factor in their recovery. Here there was a definite correlation between the clinical improvement and the administration of theelin, and where a small dose, 1–2,000 units, was unsuccessful, increase of 10,000 units was associated with pronounced improvement. All showed evidence of ovarian dysfunction with, in one case, additional hyperthyroidism. Obvious signs of endocrine upset were present in four out of five, and fewer additional factors were ascertainable in this group than in any other. The action of theelin appeared to have a specific quality. Certain features in these cases are of interest. Excepting the patient with artificial menopause none of these women was childless, and their relation to their children was good. In none of them had there been an adverse childhood environment with its stultifying effects, and in only one could direct inheritance be implicated, and that incidentally in the case of longest duration. Evidence of financial strain was provided in not more than one instance, and bereavement figured in none. The onset, coinciding with the menopause, was rapid in four, and the psychosis lacked nothing in severity, two patients having attempted suicide, and a third being considered actively suicidal. It seems likely that endocrine dysfunction was of major import in this group, and that the improvement of the internal milieu consequent on the provision of oestrogen resulted in betterment of the mental state.

Coming to the second group, there were eight patients in whom oestrogen appeared to confer some benefit. The impression was obtained that oestrogen acted by accelerating a convalescence already in evidence, and by producing a sense of increased confidence. Improvement could in no case be compared with that seen in the first group (even though doses as high as 100,000 units were given), and whilst four of these patients were ultimately discharged, there appears considerable likelihood that this would have occurred in any case. At the time of treatment the physical concomitants of the menopause had passed off in five of the eight, and were in process of subsiding in two others. The operation of additional factors was more pronounced in this group, and included adverse childhood conditions in three, and abnormal heredity in six. It seemed probable that here a purely glandular dysfunction was not the essential element.

Belonging to the category not improved after oestrogen were four patients. Three were of the ovarian type, one showing hyperthyroidism as well, and in three the endocrine upset was prominent. Nevertheless, although such large doses as 100,000 units were employed, and even though theelin, augmented by hexoestrol, was administered up to a total of over two million units, no change in the mental state was discernible. It is perhaps significant that it was precisely here where the greatest accumulation of adverse factors occurred. Commencing with the hereditary equipment, of two cases the fathers were chronic drunkards; the first mother was likewise an alcoholic, and the second was an involutional melancholic who committed suicide; a third of this series had a bad family history of mental deficiency. Childhood again was particularly adverse in three. The two married women were poorly adjusted, one manifesting frigidity coupled with a morbid fear

of pregnancy, whilst of the single women one had lost her fiancé, and the other had probably planted the seeds of her delusions of sin and disease in her earlier promiscuity. Factors additional to these were present in all. It seems feasible that the endocrine element was outweighed by the aggregation of influences prolonged in their application and pernicious in their effect, and this, therefore, may be the reason why endocrine treatment failed to elicit a response.

The final group, where a deterioration followed oestrogen therapy, comprised three members. A dose of 1,000 units produced little response, but when the individual dose was increased to 10,000 units and a total dosage of 100,000 units administered within a period of two weeks, a striking increase in agitation became apparent in all three cases. Depression deepened, delusions appeared more prominent, and in one patient a suicidal tendency manifested itself. An examination into the earlier history failed to reveal any particularly deleterious influence. Childhood had been uneventful in all, whilst abnormal heredity affected only one, and although other factors were present, their operation on the whole did not appear of particular intensity. When, however, the endocrine state was considered it was found that all belonged to the category of pluriglandular insufficiency and that two were undergoing the menopause, whilst the third, aged 45, may have been rapidly approaching this phase. Two were hypothyroid and the third hypo-adrenal.

Oestrone has been shown to produce hypofunction in the thyroid (18) and degeneration in the suprarenal cortex (19), and the further depression of these already underactive organs may well have been mirrored clinically in the mental state. On this assumption thyroid was administered to the first two and adrenal cortical hormone to the third, and in all three the mental state improved. One hypothyroid recovered and was discharged after two months. The other showed improvement only after six months, but although allowed home for four-day periods was not considered well enough for discharge; incidentally it was in this member of the group that the greatest number of adverse factors were ascertained. The hypoadrenal patient responded rapidly to adrenal cortex hormone and became bright and cheerful, but invariably relapsed as soon as the injections were discontinued.

Commentary.

In the preceding study an attempt has been made to evaluate endocrine therapy in relation to the recovery and improvement-rate, and the results have tended to show that in most cases a favourable outcome could not be attributed to any one factor.

With regard to oestrogens it was felt that a classification of patients according to response to treatment could be made out, and that this gave more accurate information of the relative importance of the part played by oestrogens in improvement or recovery. It was found possible to form four groups: those where oestrogen led to a pronounced improvement; those where a slight improvement resulted; those where no change occurred; and the group that was worse after oestrogen.

In five cases the administration of oestrogen was followed by a marked advance and recovery, and it seemed equitable to attribute to this treatment a large share of the credit. In 25 per cent., therefore, recovery appeared mainly due to oestrogen. Eight patients were benefited, the effect being apparent either in a slight lessening of depression, or in the improvement of cases where the severity of the psychosis was already diminishing. Although four of this group were ultimately discharged recovered several factors were operative in all, and the part played by oestrogen in no way corresponded to the specificity of action observed in the first group.

In the third group were four patients who showed no improvement even though receiving much larger doses than had the cases who recovered. Further comparison showed that adverse factors other than those of an endocrine nature reached their maximum in this group, and it appeared possible that the lack of response to oestrogen was due to the malignancy of these factors. Conversely, those cases which responded well belonged to that group where the minimal number of such factors could be ascertained.

Claims for the efficacy of larger dosage could not be substantiated from this series. The patients of the first group, all of whom recovered, received a total

dosage varying from 32,000 to 254,000 international units, and in the latter case spread over months. Those cases which remained unimproved received much greater doses, one patient getting as much as 2,000,000 units in the space of a fortnight. The impression was conveyed that if a patient did not respond to a moderate dosage the exhibition of massive dosage was unlikely to be more successful.

Three patients were worse after treatment, and here an endocrine mechanism appeared definitely implicated. Polyglandular insufficiency was shown to be present, and it seemed that oestrogen, by upsetting still further the hormonal balance, brought about the deterioration in their state. The adverse results reported by others are explicable on such a basis. The administration of thyroid led to recovery in one and ultimate improvement in another, whilst suprarenal cortex hormone produced transient improvement in the third.

This study further illustrates the complex aetiology of involutional melancholia. Where an element of endocrine dysfunction was definitely present, and particularly where it was marked, the impression was conveyed that the glandular disturbance was of importance in contributing to the full development of the psychosis. Nevertheless, other factors were also present. Throughout the normal personality of these patients there kept recurring a tendency to be easily worried, sensitiveness, marked conscientiousness, lack of sociability, and timidity, so that these seemed characteristic of the usual prepsychotic personality. The prevalent physical type was the asthenic, in contrast with the general findings in manic-depressive psychoses. Heredity and environment also played their part. Direct parent-daughter transmission, including two instances of involutional melancholia, occurred in 30 per cent. of cases, whilst other 30 per cent. showed tainting and a preponderance of cases developed in a rural setting. The good prognostic value attributed to a happy family life seemed justified from the increased recovery-rate in the patients belonging to this series.

The existence of adverse physical and psychical factors could be demonstrated in the majority of the series, and their cumulative effect might well have been of considerable importance in the origin of mental illness. From the examination of this series it seemed that whilst the glandular factor was of considerable importance, no one factor, whether glandular or otherwise, was capable of inducing the typical picture of involutional melancholia. In most cases there was present a constellation of factors including endocrine upset, a particular physical type, hereditary weakness, unhelpful personality trends, and other adverse physical and psychical conditions.

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