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AN ANALYSIS OF PSYCHOSES ASSOCIATED WITH GRAVES' DISEASE.*

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The not infrequent occurrence of a psychosis in the course of Graves' disease gives rise to such questions as: Is there a relation between the Graves' disease and the psychosis? If so, what is that relation? Do the psychoses occurring under such circumstances correspond in character to the various recognized psychoses, or do they show such characteristics as should entitle them to special classification? What is the prognosis in such cases? etc.

With the hope of answering these and some other questions I have undertaken an analysis of 82 cases presenting psychoses associated with Graves' disease. A few cases were patients at the McLean Hospital; most of the cases were collected from the literature.

As is well known, the diagnosis of Graves' disease is frequently made without the presence of all the classical physical symptoms, and frequently when the symptoms are very slight, so much so at times as to make the diagnosis doubtful. Among the cases to be here considered, however, the physical symptoms were in each instance tolerably well marked.

The interest in Graves' disease has for many years been considerable, and its frequent association with a psychosis has been noted. Many articles with reference to its etiology, and especially with reference to its treatment, have been written, and have aroused considerable interest. Many of the authors, however, have been general medical men or surgeons, and the psychiatric

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side of the question has been comparatively neglected. For many years such psychoses as were observed were considered to be the direct result of the Graves' disease, and have often been classified as Graves' psychosis. In text-books of psychiatry usually little or nothing is to be found concerning this subject. More recently attempts have been made to answer some of the questions above, and the analyses of a few cases here and there have given rise to some doubt as to the direct relationship between Graves' disease and the psychoses associated with it. Numerous opinions have been expressed, some to the effect that both the Graves' disease and the psychoses had a common etiology based upon auto-intoxication or inherited degeneracy; and some, recognizing the similarity between many of the psychoses seen with Graves' disease and in manic-depressive insanity, have gone so far as to suggest that in all cases of manic-depressive insanity we have as an etiological factor some disease of the thyroid. It will not be attempted to discuss these various theories, but merely to present an analysis of the cases collected and to draw some conclusions from the results.

The present collection of 82 cases includes 20 men and 62 women. In dealing with them, the fact was at once striking that of the 54 cases in which the heredity was stated, 63% showed a heredity for mental disease. In six cases there was also heredity for Graves' disease. In 26 cases, 32% of the total number, there were evidences of a neurotic or psychopathic make-up, and this figure is probably much too low, since in many cases no sufficient data were given to allow one to judge concerning this point. In this same connection is to be noted that 12 cases, 15% of the total number, had had psychoses previous to the onset of any objective symptoms of Graves' disease. Two had had more than one previous attack; in one case a psychosis had preceded the Graves' disease by two years, in one by eighteen years, in one by seventeen years, in two by five years, in one by four years, and in the remaining six the exact time was not given.

The age at onset of the Graves' disease varied from 18 to 63 years, the average being 33.9 years. Likewise the age at onset of the psychoses showed a wide variation, 18 to 66 years, the average being 35.8 years. That is, the psychosis came, on an average, about two years after the Graves' disease.

A more careful examination of the intervals gives some interesting information. In 22 cases the interval was not given. In 32 cases the onset of the Graves' disease and the psychosis was practically simultaneous. Among the remaining cases a one-year interval was noted in three, a two-year interval in five, a three-year interval in eight, a five-year interval in four, a six-year interval in one, an eight-year interval in two, and a ten-, eleven-, twelve-, thirteen- and twenty-year interval in one case each. That is, in 32 cases, or 52% where the interval was known, the onset of the Graves' disease and the psychosis was practically simultaneous, in the remaining 48% the curve of the intervals rises rather quickly to three years, and then falls again more slowly. This at once suggests the question of whether or not we are dealing with two different kinds of cases. A further analysis shows that 85% of the simultaneous cases had a bad heredity, as against 36% of the cases where the psychosis was later in onset, or from the opposite standpoint, only 15% of the simultaneous cases had a good heredity, while a good heredity was found in 36% of the cases with a later onset of the psychosis. It is also interesting to note that 50% of the simultaneous cases had a bad make-up, while only 26% of the cases with later onset of the psychosis had a bad make-up. Again, 19% of the simultaneous cases had had previous psychoses, while only 11% of the cases with later onset of the psychosis had had previous attacks. In regard to the various symptoms noted in the psychoses of the two classes, i.e., the simultaneous cases and those with later onset of the psychoses, there is not sufficient variation for significance.

If we turn next to a consideration of the more striking symptoms shown in the psychoses of all cases, we find that there was a depression in 53 cases, 65%; excitement in 51 cases, 62%; delusions in 40 cases, 49%; apprehensiveness in 37 cases, 45%; irritability in 33 cases, 40%; exhilaration in 23 cases, 28%; hallucinations in 23 cases, 28%; incoherence in 13 cases, 16%; delirium in 11 cases, 13%; seizures in 8 cases, 10%; memory defect in 7 cases, 9%; paraphasia in 3 cases, 4%; phobia in 3 cases, 4%. (Cf. the table, p [8a].)

A study of the depressions shows that at some stage of the psychoses 23% of them showed exhilaration, and what is more striking, 58% and 59% of them showed, respectively, excitement and

apprehensiveness. Such a combination of symptoms, while often seen in cases at the involution period, is rather striking in such a large percentage of cases whose average age is about 35 years. 51% of the depressions were deluded, which is perhaps of no great significance. 45% of the depressions were notably irritable, perhaps a larger percentage than would be seen in depressions in general.

Of the 23 cases showing exhilaration, 52% at some time in the course of the psychoses were also depressed. This leaves a comparatively small percentage of the whole number, only about 12%, who showed only an exhilaration without a depression. 100% of the 23 exhilarations showed excitement; i. e., if we may be allowed to speak in terms of manic-depressive insanity, we found among the depressions a great tendency to mixed states characterized by depression with motor activity, whereas among the exhilarations we found no tendency to the opposite kind of a mixed state—manic stupor—exhilaration without motor activity. Furthermore, there was a high percentage of irritability, that symptom being present in 61%.

From the standpoint of excitement, of the 51 cases showing this symptom, 61% were depressed, and 45% exhilarated, again emphasizing the large number of mixed states where depression was associated with motor activity. Under this heading we again notice a high percentage of irritability, 51%, as might perhaps be expected. Apprehensiveness occurred in 43%, and delusions in 48%. These figures are mentioned because they occur among the higher percentages, rather than because of any special intrinsic significance.

Considering the 33 cases with irritability, we may briefly note that 79% of them were excited and 66% depressed, again indicating the prominence of these symptoms from another viewpoint.

From the standpoint of apprehensiveness, 86% of the 37 cases showing this symptom were, as might be expected, depressed. 59% were excited, 54% deluded, and under this heading we for the first time find hallucinations rising to a large percentage, viz.; 41%.

Twenty-three cases, 28% of the total number, had hallucinations, mostly of hearing, some of sight, and what is perhaps particularly striking is that 70% of these cases were depressed. Otherwise nothing special stands out under this head.

Forty of the cases had delusions, 68% of these were depressed, 62% excited, 62% apprehensive, 50% irritable. This seems to emphasize the prominence of apprehensive delusions.

The 13 cases showing marked incoherence showed also, as may be expected, a large percentage of excitement and exhilaration, with 62% irritable.

Only 11 cases had a marked delirium, and in this connection only two high percentages are to be noted: 91% were excited, and what is more significant, 82% died, the highest per cent of deaths recorded under any heading.

The number of cases with memory defect, seven, is too small to make an analysis of any value. It is perhaps interesting to note that two were under 30 years of age, one was 32 and had had seizures, one was 43 and had become demented in about six months, one was 48 and was paraphasic; the other two were 43 and 46 years of age, respectively, showing that the memory defect could not be ascribed to senility, and in half of them at least there was slight probability of arteriosclerosis.

Paraphasia was noted in only three cases; all were decidedly irritable. No other characteristic was common to more than one case.

Phobias were also noted in three cases, and they were simply apprehensive and depressed.

Eight cases had had seizures; four were exhilarated and four depressed. 87% were excited. The ages here again indicate that on the whole they were rather young; thus two were under 20, four were under 35, one was 42, and one 66 years of age. Five of these cases died within a comparatively short time, the second highest percentage of deaths noted under any heading.

When it comes to a consideration of the outcome, the great majority of cases passed from observation in an unimproved condition and the further course is unfortunately not known. Four cases improved; they had all been excited and irritable. Three of them had been both exhilarated and depressed. In one case the mood was not mentioned as either exhilarated or depressed, but improvement followed after two years of excitement. In three other cases the exact durations were not given. The ages in these cases which improved were 18, 20, 31, and 35 years.

Ten cases recovered from their psychoses; eight had shown a

depression with excitement, one an exhilaration with excitement, and one an exhilaration followed by a depression with excitement. In two of these recovered cases the Graves' disease and the psychoses had come on practically simultaneously as the result of taking thyroid, and in both cases the physical symptoms had disappeared on the withdrawal of the drug. In the remaining eight cases the mental symptoms disappeared without corresponding disappearance of the physical symptoms. In three cases there was no improvement noted in the physical symptoms, in five cases a partial improvement. The ages of these recovered cases were 23, 24, 27, 30, 37, 43, 53, and in the three remaining cases the age was not given. The hereditary data in these cases indicated little. In three there was a bad heredity, in four a good heredity, and in three the data were wanting.

Only two cases were known to have demented. Both began with apprehensive depressions and one became delirious. The ages were 26 and 43. 25 cases, or 30% of the total number, died under observation, quite a large proportion considering the fact that so many passed from observation in a comparatively short time. 88% of them had been excited, and under the heading of excitement we noted that 43% of the excitements died, the third highest mortality noted under any heading, the highest being, as above noted, 82% of the delirious cases, and the second highest, 75% of the cases with seizures. 52% of the deaths had shown depressions and 32% exhilarations; 36% had been apprehensive, and 24% had had seizures. Among those that died the average duration of the psychosis was thirteen weeks, the median duration was six weeks. Four cases died within a week, four within two weeks, three within a month, six within two months, three within three months, one within a year, and one within two years. In three cases the duration was not known. The ages varied from 18 to 62 years, the average being 35 years. Three were under 20, five under 30, five under 40, seven under 50, one under 60, three under 70. In regard to heredity among the cases described, the figures are too small to be of much account. In ten of the 25 information was wanting; in the remaining 15, ten had a bad heredity and five a good heredity.

Such, then, are some of the most important statistical data gleaned from the analysis. In order that anyone may make use

of the figures for his own deductions, the accompanying table is subjoined.

CORRELATION OF SYMPTOMS IN 82 CASES OF GRAVES' DISEASE.

[Per cent of cases showing the symptoms given in vertical column, also characterized by the symptoms in horizontal column below.]

	Total number of cases showing—	Per cent of cases showing—	Depression.	Exhilaration.	Excitement.	Irritability.	Apprehensiveness.	Hallucinations.	Delusions.	Incoherence.	Delirium.	Memory defect.	Paraphasia.	Phobia.	Seizures.	Improved.	Recovered.	Demented.	Died.
Depression.....	53	65	100	23	58	40	59	30	51	11	8	8	2	4	8	6	15	4	26
Exhilaration.....	23	28	52	100	100	61	43	30	48	39	17	9	4	0	18	13	13	0	86
Excitement.....	51	62	61	45	100	51	43	24	48	20	20	6	2	0	14	8	16	2	43
Irritability.....	38	40	66	42	79	100	39	23	65	26	16	18	6	0	19	13	10	3	33
Apprehensiveness.....	37	45	86	27	59	32	100	41	54	11	14	14	3	8	5	5	14	5	24
Hallucinations.....	23	28	70	30	52	30	65	100	70	9	4	9	0	0	9	4	13		17
Delusions.....	40	49	68	27	62	50	52	40	100	17	12	15	2	0	10	5	12	5	37
Incoherence.....	13	16	46	69	77	32	31	15	54	100	23	15	8	0	23	15	23	0	23
Delirium.....	11	13	36	38	91	36	45	9	45	27	100	0	0	0	9	0	0	9	32
Memory defect.....	7	9	57	29	43	57	71	29	36	29	0	100	14	0	14	0	0	14	14
Paraphasia.....	3	4	33	33	33	66	33	0	33	33	0	33	100	0	0	0	0	0	33
Phobia.....	3	4	66	0	0	0	100	0	0	0	0	0	0	100	0	0	0	0	0
Seizures.....	8	10	50	50	87	75	25	25	50	37	12	12	0	0	100	12	0	0	75
Improved.....	4	5	75	75	100	100	50	25	50	50	0	0	0	0	25	100	0	0	0
Recovered.....	10	12	80	30	30	30	50	30	30	0	0	0	0	0	0	0	100	0	0
Demented.....	2	3	100	0	50	50	100	0	100	0	50	50	0	0	0	0	0	100	0
Died.....	25	30	52	32	38	44	36	16	60	12	36	4	4	0	24	0	0	0	100

Examples: Of the 53 cases, 65%, showing depression, 100% of course showed depression; 23% exhilaration; 58% excitement; 40% irritability, etc.

The results are not only difficult of interpretation, but in some instances to a certain extent contradictory, and undoubtedly capable of different interpretations. The following are what seem to the writer to be among the more probable.

As is already noted, there is a heredity for mental disease in 63% of the cases, which is undoubtedly high; even in manic-depressive insanity, where we find the largest hereditary predisposition, according to Kraepelin, it is present in only 80%. Since we are here considering the relation of the psychoses to a physical disease, we can perhaps best compare the hereditary statistics with those of general paralysis, since we have there also a psychosis associated with a definite physical change. The statistics for mental hered-

ity in general paralysis vary greatly according to different men. Kraepelin finds a heredity in about 50% of his cases; Pilcz in only about 18% of his cases, and a fair average may be about 40%. On this basis it seems fair to assume that the mental heredity is strikingly large in our cases. With a mental heredity, then, in 63% of the cases, and a psychopathic or neuropathic make-up in 32 of the cases, together with the fact that 15% of them have previously had a psychosis, it does not seem unreasonable to conclude that we are dealing with individuals in whom a psychosis might have been expected to develop even in the absence of Graves' disease, perhaps without any tangible cause, or at least with only such causes as appear to be of etiological significance in the ordinary functional psychoses. That is, the Graves' disease is only an exciting cause, although perhaps an especially strong one.

At first glance, the fact that in 32 cases the onset of the psychosis was practically simultaneous with the onset of the Graves' disease, might be taken to indicate that etiological relationship was much stronger. It is among these simultaneous cases, however, that we find the highest predisposition to mental disease; 85% of them showing bad heredity, as against 36% of the cases with later onset of the psychosis; and only 15% of the simultaneous cases show a good heredity, as against 36% with good heredity among those with a later onset of the psychosis. Again, it will be remembered that 19% of the simultaneous cases had had previous attacks, as against 11% of the cases with the later onset.

The fact that, among four improved and ten recovered cases, the improvements and recoveries from the psychoses in all but two instances took place without any or only slight improvement in the symptoms of Graves' disease, argues against any fundamental relation between Graves' disease and the psychosis. The two exceptions were cases where thyroid had been taken and where both the physical and mental symptoms disappeared on withdrawal of the drug. The inference to be drawn from these two cases is perhaps somewhat contradictory to the above, and seems to indicate a very definite relation between cause and effect, but after all we are here dealing with an artificially produced condition.

Unfortunately the statistics of any considerable number of cases are not at my command concerning the proportion of cases with

Graves' disease which never develop a psychosis. It seems very probable that many cases, at least, go for years without psychoses, and even among the cases here considered the interval was in several instances from ten to twenty years. Syllaba, in a paper on the prognosis in Graves' disease, while not considering the psychiatric side to any extent, yet notes in a general way improvement and recovery in 62% of 50 cases which he followed throughout their lifetime.

In view of the facts already presented it would seem that in a majority of cases where a psychosis does develop, the time of origin of the psychosis after the onset of the Graves' disease is somewhat proportional to the predisposition of the individual to insanity, the most susceptible losing their mental balance at once. We must, of course, acknowledge that the strength and quantity of toxins, if such be present, may vary in different cases and have its own significance. Objectively, however, the physical and mental symptoms are not always proportional.

Finally, we must consider the possibility of common etiology for both physical and mental symptoms. Until we know more about the etiology of Graves' disease and the etiology of abnormal mental conditions, this question can hardly be settled. In many cases the course of the physical and mental symptoms is sufficiently independent to make it at least questionable.

Before leaving the etiological considerations attention may be called to the fact that among general medical men there is a tendency to consider mental grief and worry as a possible etiological factor in Graves' disease. In the cases here considered, for the most part no such condition preceded the Graves' disease, but accompanied or followed it.

If we turn next to a consideration of the mental picture in the psychoses associated with Graves' disease, we find a predominance of certain symptoms, depression, apprehensiveness, irritability, and excitement, characteristics which are usually found to a lesser degree in the sane with Graves' disease. On the whole we find that the mental pictures may vary greatly; there were many cases essentially depressions, some essentially exhilarations and vice versa, others showed in their course depressions followed by exhilarations, and still others were essentially delusional conditions. There were some cases of acute delirium; practically as much variation as is

found in the functional psychoses not associated with Graves' disease. It is interesting to note that only two cases demented, and that on the whole the course of the psychoses, apart from the prominence of hallucinations, does not resemble that of dementia præcox. In one of my own cases, however, which has had three acute attacks with perfect recovery, so as to resume her work as a school-teacher in the intervals, the mental picture was strikingly dementia præcox like. Not only were hallucinations prominent, but the mood was more or less apathetic, autochthonous ideas and ideas of reference were prominent to a marked degree, and there were many impulsive acts, and other phenomena of disintegration of the personality. The course alone was not typical, and now after about ten years the patient is in no way demented. A large number of the cases were depressed and a greater part of the depressions showed a motor activity instead of a retardation. Apprehensiveness and irritability were unusually frequent, and hallucinations were much more common than is usual in depressions. The prominence of this latter symptom suggests the possibility of strong toxic influences.

With regard to the outcome, while some cases improved and more recovered, on the whole the prognosis of the mental symptoms associated with Graves' disease seems to be more serious. In many instances the Graves' disease seems to furnish enough to produce at least chronicity, although few dementias. The rapidity with which death followed the onset in many cases was quite striking. In these cases delirium and excitement were conspicuous and the death rate much larger than in the ordinary manic excitements, even of similar severity, and it seemed much more difficult to cope with the exhaustion. It would for this reason seem probable that in addition to the exhaustion from the excitement there is some direct toxic influence from the Graves' disease which is of considerable prognostic significance.

I would conclude briefly that in many cases Graves' disease is rather an exciting than a fundamental cause of the psychosis, and that the psychoses themselves are not essentially different from the ordinary recognized functional psychoses, except as modified by the prominence of those symptoms seen to a lesser degree in the sane with Graves' disease. The prognosis is on the whole much more grave and is especially bad in the delirious cases.

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