

BIOCHEMICAL COMPONENT OF THE MANIC-DEPRESSIVE PSYCHOSIS*

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The conception that overfunction of the adrenal gland might be in some way related to the manic phase of manic-depressive cycles is not a new idea. Otto Folin attempted to demonstrate the presence of adrenalin in the circulating blood of manic patients but was unable to do so. The work of Walter B. Cannon in regard to the physiology of the adrenal gland and the sympathetic nervous system and his studies of rage reactions in the cat might lead one logically to speculate regarding what bearing his work might have upon manic psychoses.

Since investigators such as Folin have failed to prove that there is any overfunction of the adrenal medulla, it occurred to the writer that it might seem rational to search for evidence of increased amounts of the adrenocortical hormone in the blood of patients acutely manic. This line of investigation seemed all the more reasonable in view of the fact that pathologic studies have shown evidence of cortical hyperplasia in manic-depressive patients. According to the work of Lewis at the Saint Elizabeth's Hospital, in autopsy studies of manic-depressive patients, "the adrenals generally exhibit cortical hyperplasias." This line of reasoning led to the following experiments:

METHOD

Citrated whole blood from manic patients was injected daily by the intraperitoneal route into adrenalectomized cats for the purpose of determining whether or not these injections might lengthen the life of these animals in a manner similar to that induced by the cortical hormone. Blood collected from normal subjects and citrated in the same manner was injected into control adrenalectomized cats, and again the span of life following adrenalectomy was studied. An important premise to these experiments is the known fact concerning duration of life in cats following adrenalectomy. The average duration in 18 cases reported by Marine and Baumann was 5.3 days, and the average in 9 cases reported by Hartman was 5.7 days (Hartman, et al.) It may be noted that the figures by these two groups of workers are closely similar.

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Blood specimens were collected when possible every two to three days. All specimens were chilled promptly after collection and kept in the refrigerator. That fraction of blood used for each injection was warmed just prior to use but the main reservoir of blood was kept at refrigeration temperatures at all times in order to discourage chemical changes. One experiment with rats was performed. The procedure was the same as with cats except for the fact that smaller intraperitoneal injections were employed.

RESULTS

The first experiment with cats was remarkable. The cat receiving normal blood was dead in 48 hours. The cat receiving blood taken from a manic patient was alive and in good condition after 48 hours, and was still so after three days, at which time he began to eat. (Normally adrenalectomized cats do not eat from the day of operation until death.) Later this cat ate voraciously and exhibited convincing evidence of unusual strength. Gradually it became more and more difficult to restrain the animal at the time of injection and on one occasion it required the combined efforts of three of us to perform the intraperitoneal injection. Usually, a striking observation regarding adrenalectomized cats is the fact that, whereas before operation they can jump easily from the floor to an elevated surface such as a table, they become very weak after operation, they walk in a slow, unsteady manner and they can no longer perform the normal feats of leaping. This cat lived for 19 days—14 days beyond his expectancy, and finally died in convulsions on the 19th day. A very interesting feature of this cat was the fact that he became highly excitable, was easily enraged and when we would bang on the cage door, his pupils would dilate widely, he would responsively spit, bare his fangs and slap with his paw at the cage door. It is interesting to note that this animal with both adrenals removed was capable of marked rage reactions.

In subsequent experiments none of the cats treated with "manic blood" showed any signs of nervous excitability and none of them exhibited rage reactions. However, the average duration of life in experimental animals was 5 times as long as the average of control animals in the first series of animals studied.

No organized attempt was made to study the muscular strength and endurance of adrenalectomized cats receiving healthy and manic blood. Usually the cats were removed from their cages only for purposes of injection and for weighing them. One cat receiving manic blood, as already described, had a degree of strength so far above that seen in the usual adrenalectomized animal that it was impossible to overlook these observations. In fact, this cat seemed to have strength much above that of normal cats. A second cat receiving manic blood was discovered quite by accident to have unusual strength and endurance. On the seventh day following adrenalectomy and after the seventh injection of manic blood this cat was being transferred from Harvard Medical School to a laboratory at McLean Hospital. He had

not accepted food since the day of operation. Suddenly this cat leaped from the grasp of an assistant who was holding him and bounded away at top speed, running without apparent fatigue for a distance of approximately 250 yards. At no point during this run did he seem to lessen his speed. He was finally cornered between a wall and a building and caught. At the end of this run the cat was found to be in quite good condition, showing no signs of fatigue except for palpitation. A performance such as this is certainly far beyond what one would ever expect in an adrenalectomized cat or in any cat at the end of a week without food.

The first experiment with rats was also remarkable. Five adrenalectomized rats were employed. Two of these received intraperitoneal injections of "manic" citrated whole blood, given twice daily in dosage of 2 cc. at each injection. Three of these adrenalectomized rats served as controls and were given intraperitoneal injections of normal citrated whole blood in the same manner and in the same dosage. The rats receiving manic blood were very strong and active and were hard to manage during injections. The rats receiving normal blood were weak and wobbly and were easily held for the injections. The rats receiving "manic" blood were in a constant state of activity, noticeably in contrast with the control rats which remained conspicuously quiescent from the time of operation until death. One rat receiving "manic" blood showed a marked diarrhea; this is said to be very rare in adrenalectomized rats, and might be compared to the diarrhea of manic patients. The 2 rats receiving "manic" blood lived 7 days and 25 days, respectively, an average of 16 days. It was the rat with diarrhea that lived only 7 days. The 3 rats receiving normal blood lived 3 days, 1 day and 2 days respectively, an average of 2 days. The average duration of life of experimental animals, therefore, was eight times as long as that of the controls.

The first experiment was done with rats, but following this, cats were used exclusively because of the evidence that accessory adrenal tissue is much more common in rats than in cats. Therefore, survival experiments seemed more reliable in the latter. Recent evidence, however, tends to indicate that the presence of accessory adrenal tissue in rats has been overestimated.

TABLE 1.—"MANIC" BLOOD SERIES—RATS

<i>Rat No.</i>	<i>Duration of Life following Adrenalectomy</i>	<i>Autopsy Findings</i>
1.....	7 days	No accessory adrenal tissue found
2.....	25 days	
Average: 16 days		
<i>Controls Using Normal Blood—Rats</i>		
3.....	3 days	No accessory adrenal tissue found
4.....	1 day	
5.....	2 days	
Average: 2 days		

Rats receiving "manic" blood were very strong and were hard to manage during injections.

Rats receiving "normal" blood were weak and wobbly—easily injected.

In this small series, the average duration of life in experimental animals was eight times as long as that of controls.

FIRST SEVEN "CAT" EXPERIMENTS

Those receiving citrated "manic" whole blood by intraperitoneal injections daily.

<i>Cat No.</i>	<i>Length of life following Adrenalectomy</i>
1.....	19 days
2.....	12 days
3.....	9 days
4.....	6 days
	Average duration, 11.5 days

Those receiving citrated normal whole blood by intraperitoneal injection daily (blood from timid, subnormal human subjects).

<i>Cat No.</i>	<i>Length of life following Adrenalectomy</i>
5.....	2 $\frac{1}{3}$ days
6.....	2 $\frac{1}{2}$ days
7.....	2 $\frac{1}{3}$ days
	Average duration, 2.3 days

Therefore, the average duration of life in experimental animals in this series was 5 times as long as the average of controls.

Following the experiments involving the first 7 cats, an epidemic of snuffles broke out and so many normal cats died in their cages that it did not seem fair to draw final conclusions regarding the length of life following adrenalectomy, particularly in view of the fact that almost all cats following adrenalectomy died with snuffles, which is a serious illness in cats and is often fatal. However, the results of these experiments were interesting. The duration of life following adrenalectomy in cats receiving manic blood was only slightly less than in the first series and might conceivably have been much longer if the animals had remained healthy.

Second series of cats receiving manic blood by intraperitoneal injection daily.

<i>Cat No.</i>	<i>Length of life following Adrenalectomy</i>
8.....	8 days
9.....	11 days
10.....	14 days
11.....	11 days
12.....	12 days
13.....	10 days
14.....	6 days
Average duration, 10.3 days	

Two cats receiving manic blood died with severe snuffles shortly after adrenalectomy.

<i>Cat No.</i>	<i>Length of life following Adrenalectomy</i>
15.....	5 days
16.....	3 days
Average duration for both groups, 9 days	

Control cats receiving intraperitoneal injections of citrated whole blood from vigorous normal subjects in a state of emotional excitation.

<i>Cat No.</i>	<i>Duration of life following adrenalectomy</i>
17.....	4 days
18.....	8 days
Average duration, 6 days	

In this series of experiments the cats receiving manic blood lived only 50 to 70% longer than control cats injected with the blood of vigorous normal subjects in a state of emotional excitation. However, in this same series of experiments, the average duration of life of cats receiving manic blood was 100 to 130% longer than that of cats receiving mammalian Ringer's solution by intraperitoneal injection.

TABLE 2.—CONTROL EXPERIMENTS USING MAMMALIAN RINGER'S SOLUTION INJECTED INTRAPERITONEALLY

<i>Cat No.</i>	<i>Duration of Life Following Adrenalectomy</i>	<i>Amount of Ringer's Solution Injected</i>
19.....	6 days	10 cc. first 2 days 5 cc. daily 4 days
20.....	3 days	10 cc. first 2 days 5 cc. on 3rd day
Average duration, 4.5 days		

Regarding the depressive phase of manic-depressive psychosis, one experiment was performed. A 500 cc. transfusion of citrated whole blood was taken from an acutely manic patient and given to a patient in a profound depression. No effects were observed. It is clear that the transfusion showed no tendency to correct any supposed hypocortinism. This experiment led us to distrust the interpretation of the depressive psychosis as an adrenal gland underfunction.

The dosage of citrated whole blood employed in the experimental series of cats as well as in the control series was usually 5 cc. for each intraperitoneal injection. In some of the experiments wherein cats receiving "manic" blood survived for long periods of time, it became necessary to reduce the frequency of injections and to reduce the dosage of each injection to 2 cc. or 3 cc. on account of a reduced supply of blood. The available reservoirs of manic blood were sometimes unexpectedly reduced by recovery of the patients. There was never any shortage of normal blood and the dosage of it was always kept at exactly the same level as that employed with the manic blood used in concurrent experiments. Intraperitoneal injections of 10 cc. doses of normal and manic blood were well tolerated.

DISCUSSION

These experiments have provided biological evidence that the blood of manic patients may differ from the blood of healthy subjects. The experiments were carried out to ascertain whether or not it might be possible to demonstrate in the blood of manic patients an increase in the circulating cortical hormone. It is not assumed that these experiments have proved this to be the case. It is assumed only that evidence has been found to indicate that adrenalectomized animals when injected with manic blood behave differently from similar animals injected with healthy blood. What the chemical difference between the two bloods may be remains to be discovered. The most striking observations in this series of experiments are in reference to the strength and activities of 2 of the rats and 2 of the cats injected with the blood of manic patients. A search for further evidence regarding the nature of this effect would surely seem justifiable.

This paper is preliminary in nature but is published at this time because of the necessity of postponing further experimentation for an indefinite and uncertain period of time. Many more experiments and control studies should be done. However, the experiments have been difficult and very time-consuming. Nothing can be done except at times when acutely manic patients are available for study. Blood specimens must then be collected at frequent intervals and transported promptly to the physiological laboratory where the adrenalectomized animals must be ready for use. Only the acutely manic patients seem ideal for diagnosis and study, and since the acutely manic patients often recover in a short time, the supply of manic blood may become unexpectedly eliminated. The collection of blood from patients acutely manic is hampered at times quite naturally by failure of the patient to co-operate.

Perhaps this report will stimulate added interest in the manic psychosis as a physiological and general medical problem rather than as a purely psychological one. It may be hoped that other investigators will continue these studies.

The following hypothesis is offered as an interpretation of the manic psychosis: The disease is due to overstimulation of the entire autonomic nervous system with prolonged maintenance of the rage reaction type of vascular bed (Wolff and Wolf). The two sides of this nervous system including both the sympathetic and the parasympathetic are functioning powerfully but equally and homeostasis is maintained, thus accounting for the fact that the blood sugar and certain other chemical determinations in the blood show no change even in violent manics (Whitehorn). This increased activity of the autonomic nervous system involves a discharge of nervous impulses to the intestinal tract and in some way brings about increased peristaltic movements and the diarrhea usually observed in the manic. Increased nervous discharges are sent along the sympathetic nerve fibers which ascend the arterial tree leading to the anterior lobe of the pituitary gland, from which a reservoir of hormones breaks loose. These hormones from the "master gland" get into the circulation and bring about a tremendous increase of internal secretions from the thyroid, adrenals and gonads. The manic's excessive sexual drive is thus accounted for. The adrenals and the gonads would seem to dominate the pattern of glandular overactivity in the manic.

Since the cortical hormone functions in part to influence recovery from fatigue (Hartman, et al.) it is presumed that adrenocortical overactivity in the manic psychosis serves to compensate for and aid in recovery from maniacal overactivity. The relationship of the cortical hormone to recovery from muscular fatigue (Hartman) might explain the rapid recovery from fatigue exhibited in the cat naps which so quickly bring about complete recovery from long overexertion in the manic.

The interglandular relationships as studied by Baird, Cloney, and Albright in their cold room experiments provided much of the real background for the theoretical considerations which led to these researches, especially in regard to the intimate and constant influence which the anterior lobe of the pituitary seems to exert upon the function of the adrenal cortex. This line of thinking led inevitably to the assumption of pituitary overfunction after discovery of evidence of adrenal cortex overfunction in the manic.

CONCLUSIONS

(1) In these experiments an attempt has been made by means of adrenalectomized cats and rats to ascertain a rough biologic assay of the cortical hormone of the citrated whole blood of manic patients and of healthy subjects.

(2) Adrenalectomized cats, untreated, usually live on the average 5.5 days following removal of the adrenals (literature).

(3) Seven adrenalectomized cats were studied in the control series. These

received intraperitoneal injections of Ringer's solution and of the citrated whole blood of healthy subjects. The average duration of life in this series of controls was 4 days.

(4) Adrenalectomized cats receiving citrated whole blood of manic patients lived an average of 11.5 days in one group of 4 cats, and 10.3 days in a second group of 7 cats.

(5) The average duration of life of all 11 experimental cats was 2.7 times as long as the average of all 7 control cats (10.7 days versus 4 days).

(6) Two adrenalectomized rats receiving citrated whole blood from manic patients lived eight times as long as 3 adrenalectomized rats receiving citrated whole blood from normal subjects (16 days versus 2 days, average figures).

(7) In one experiment, a transfusion of 500 cc. of citrated whole blood from a manic patient to a depressive patient had no effect.

(8) One adrenalectomized cat while receiving manic blood ate voraciously and exhibited dramatic rage reactions despite absence of adrenals. This animal's physical strength was truly remarkable. A second adrenalectomized cat while receiving manic blood was discovered quite by accident to possess unusual strength and endurance. Adrenalectomized rats receiving manic blood were very strong; they were very hard to manage, and were very difficult to inject. Rats receiving normal blood were weak and wobbly and were easily injected.

REFERENCES

- Baird, P. C., Jr., Cloney, Elizabeth and Albright, Fuller: Effect of Cortical Hormone in Preventing Extreme Drop in Colonic Temperature Displayed by Hypophysectomized Rats upon Exposure to Cold, with Preliminary Observations upon the Effect of Hypophyseal and Other Hormones. *Am. J. Physiol.*, 104: 489, 1933.
- Folin, Otto: Unpublished studies done at McLean Hospital, Waverly, Mass.
- Hartman, F. A., et al.: The Hormone of the Adrenal Cortex. *Am. J. Physiol.*, 86: 353, 1928.
- Hartman, F. A., and Thorn, G. W.: The Effect of Cortin in Asthenia. *Proc. Soc. Exper. Biol. & Med.*, 29: 48, 1931-32.
- Lewis: Cited by White.
- Marine, D., and Baumann, E. J.: Duration of Life after Suprarenalectomy in Cats and Attempts to Prolong It by Injections of Solutions Containing Sodium Salts, Glucose and Glycerol. *Am. J. Physiol.*, 81: 86, 1927.
- White, William A.: *Outlines of Psychiatry*, Ed. 12. Washington: Nervous and Mental Disease Publishing Company, 1929. P. 165.
- Whitehorn, J. C.: The Blood Sugar in Relation to Emotional Reactions. *Am. J. Psychol.*, 13: 987, 1934.
- Wolff, H. G., and Wolf, S.: Studies on a Subject with a Large Gastric Fistula: Changes in the Function of the Stomach in Association with Varying Emotional States. A. Am. Physicians, Atlantic City, N. J., May 5, 1942.

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