Blood-Sugar Studies in Mental Disorders. By S. A. MANN, B.Sc.Lond., F.I.C. (From the Pathological Laboratory of the London County Mental Hospitals, Maudsley Hospital.)

INTRODUCTION.

IT is a common experience in the investigation of mental disorders that glycosuria is frequently found, thus indicating a tendency in such cases to a faulty carbohydrate metabolism. With the exception of epilepsy, this occurrence of glycosuria has been noted in most mental conditions. Intermittent glycosuria is met with in general paralysis (Kraepelin) (1); Bond (2) and Strauss (3) note it in about 10 *per cent.* of their cases. In dementia præcox Schultze and Knauer (4) did not observe glycosuria in the apathetic form of hebephrenia, but often found it to occur with catatonic excitement. With other observers (see Allers (5)) they record the marked association of glycosuria with depressed states, while its occurrence in mania was infrequent except in markedly excited and resistive cases.

In all these instances the glycosuria appears to be dependent on the emotional state of the individual, as indicated by Mita (6) in hysteria and neurasthenia, by Von Jaksch (7), Arndt (8), and Horn (9) for traumatic neurosis, by Goodhart (10) for neurasthenia, by Travaglino (11) for catatonia and senile dementia, by Strauss (3) for imbecility, by Schultze and Knauer (4) for dementia præcox, imbecility and general paralysis. Moreover, apart from mental disorders, glycosuria is often associated with emotional states in normal individuals. Folin, Denis and Smillie (12) found glycosuria in students following difficult examinations; Cannon and Fiske (13) report its occurrence with excited spectators of a football match. Ricci (14) found a transient glycosuria in 6 out of 15 cases following the information of the necessity of an operation. Lastly, the effect of emotional disturbance, especially of a depressive character, in aggravating the glycosuria in diabetic patients is generally admitted (Van Noorden (15)).

With mental disorders attempts were made to investigate this disturbance of carbohydrate metabolism by estimating the sugar tolerance (Ehrenberg (16), Graziani (17), Lugiato (18) Trepsat (19), Heidema (20), and Raimann (21)) according to the glycosuria following glucose dosage (150 grm.). With the exception of epilepsy, in which condition Raimann records a rather higher assimilation power for glucose, the work of these observers shows a tendency to a lowered tolerance in mental conditions associated with depression, and Raimann reports the most marked lowered assimilation in melancholia.

The investigation of carbohydrate tolerance, however, must depend on three factors—the rate of absorption, the glycolytic and glycogenic functions of the organism, and the renal threshold for sugar; there may be marked variations in the renal threshold, and therefore the estimations of carbohydrate tolerance depending on

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the appearance of glycosuria after oral administration of glucose is open to error.

Attention was next drawn to blood-sugar values in various mental disorders, and the work of various observers (Weston (22), Raphael and Parsons (23), Kooy (24), Uyetmasu and Soda (25), and Wuth (26)) showed that somewhat higher fasting levels may occur in most mental conditions, but the averages fall within normal limits.

Within recent years, however, the methods for blood-sugar determination have improved in accuracy and simplicity, and it is now possible to investigate carbohydrate metabolism by the estimation of blood-sugar values at frequent intervals following the ingestion of a glucose meal.

In this work the author presents the results obtained from the blood-sugar curve following glucose dosage in 152 cases of early mental disorder admitted to the Maudsley Hospital. As will be seen later, the main finding is the frequency of an abnormally sustained hyperglycæmia following glucose ingestion. To investigate further this abnormality consideration has been given to various influences affecting the blood-sugar curve, and results will be presented showing the influence of sympathetico-mimetic drugs (adrenalin and pilocarpine), both on fasting blood-sugar levels and following glucose ingestion. The series of cases will also present examples of the action of endocrine secretions on the blood-sugar curve. In view of the theories concerning blood-sugar regulation, attempts have been made to investigate the blood diastase under various influences; and, lastly, in a following paper the results are given of the investigation of the glycogenic function of the liver by means of the lævulose test in a series of 74 cases of mental disorder, and 18 normal individuals.

Technique.

There are now a number of reliable and simple methods for the estimation of blood-sugar on small quantities of blood. Of these may be mentioned the titrometric methods of MacLean (27), and Hagedorn and Jensen (28), and the Calvert (29) modification of the Folin and Wu (30) colorimetric technique. In this investigation the latter method has been used, and was selected after careful examination of its accuracy because its simplicity enables a large number of estimations to be carried out at the same time.

The method depends on the collection of a small quantity of blood from a finger-prick, 0·16 c.c. by pipette or about 200 mgrm. weighed in a platinum capsule on a torsion balance; the blood proteins are removed with tungstic acid, the protein-free filtrate boiled with alkaline copper tartrate solution; phosphomolybdic

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acid solution is added, producing a blue colour by the interaction with, and in proportion to, the cuprous salts present. Instead of using standard glucose solutions for comparison, Calvert has analysed the colour formed by the interaction of cuprous salts and phosphomolybdic acid, and has prepared a glass colour disc, standardized for all values of glucose with a correction curve adjusting colorimeter and reduction variations. I have found the method to give reliable and accurate results, with the essential precaution that it is necessary to check the glucose values of the standard disc, not only when fresh copper and phosphomolybdic solutions are prepared, but also frequently with the same solutions.

Various criticisms of the method have been published. Rothberg and Evans (31) rightly state that the blue colour produced with the original Folin and Wu technique by the interaction of phosphomolybdic acid and cuprous salts is not exactly proportional to the amount of glucose present, correct values being only possible when the colour produced by the sugar solution to be estimated is nearly the same as that produced by the standard dextrose solution; in the Calvert technique these variations are obviated by the standardization of the colour disc for all values of glucose ,and accurate correction. Lynch (32), in a survey of blood-sugar methods, states that in his opinion it is impossible to match exactly a blue liquid with a piece of blue glass, and that comparison of the relative depths of two colours, when they are not exactly the same tint, is often very difficult. I am unable to endorse this opinion, and can only consider it as the result of superficial examination rather than reasonable experience of the method. The criticism of Stanford and Wheatley (33) relating to variations dependent upon the concentration of the alkaline copper tartrate solution and the temperature at which the phosphomolybdic acid is added have been dealt with by Calvert (29), and resulted in slight modification of the technique which has added to the accuracy and utility of the method. For the estimation of sugar in small quantities of blood collected in the platinum capsule (about 200 mg.) or in the 0·16 pipette with final colorimetric determinations against a standard glass disc, I have found the method reliable, accurate and time-saving.

The cases examined have been given a glucose meal of 50 grm. in 8 oz. of water following a twelve hours' fast. The majority were able to come to the laboratory, but were kept resting during the test. Blood-sugar determinations were made at intervals during two hours or more following the glucose ingestion.

Janney has recommended a standard glucose meal of 1·75 grm. per kilo body-weight. The theoretical meal would be about 2·5 grm. glucose per kilo body-weight, based on the findings of Janney (34) and Fisher and Wishart (35), that up to 80 *per cent.* of injected glucose is absorbed in the course of two hours, and Sansum and Woodyatt (36) that the maximum intravenous tolerance rate of

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man and animals without glycosuria is 0·85 grm. per kilo body-weight per hour. Janney's standard meal would be about 100 grm. glucose for a body-weight of 10 st., but, as will be seen later when the normal blood-sugar curve is considered, the same type of blood-sugar curve is obtained with a glucose meal from 30 grm. upwards, and larger dosage does not appear to be necessary.

Material.

The cases examined are a series of 152 patients (45 male, 107 female) admitted to the Maudsley Hospital for early uncertified mental disorders. They varied from the milder neuroses to the more acute forms of mental trouble. The acute psychotics were mainly of the depressed or stuporose types, because of the difficulty of dealing with the manic, the agitated and the impulsive. A large number of adolescents of the dementia præcox type were included, together with depressed cases of all ages.

Normal Blood-Sugar Curve.

For purposes of comparison with the results obtained in this investigation it is necessary to consider the normal blood-sugar curve. Blood-sugar levels following the administration of various sugars in varying amounts have been investigated by MacLean and de Wesselow (37) and Spence (38) in "normal" individuals at different ages. The ingestion of glucose in the fasting individual is followed by a rise in blood-sugar until a concentration in the region of 0·17 *per cent.* is reached; this rise attains its maximum in 45 minutes to one hour and is followed by a rapid fall, so that from 90 minutes to 2 hours after the glucose administration the original fasting level is attained. In the normal the maximum rise is obtained with a glucose meal of 25–30 grm.; increasing the dosage does not increase the maximum concentration, but tends to prolong the resultant hyperglycæmia, but even with a meal of 100 grm. the original fasting level is easily attained within two hours of ingestion. In the normal individual the hyperglycæmia resulting from the administration of carbohydrates lies about the level of 0·17 *per cent.*, which is the normal renal threshold for glucose, and cannot easily be forced above it. Janney and Isaacson (39) state that the absorption rate for pure glucose solutions in normals is fairly constant; also it has been shown that as much as 20 *per cent.* of a large carbohydrate meal may be recovered from the stomach after the blood-sugar has fallen to normal (Calvert (40)), and that absorption must still be proceeding. The fall, then, cannot be due to cessation of absorption, and it is assumed that the rapid drop in the normal

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curve is caused by the intervention of a storage mechanism, by a glycogenesis which stores the sugar at a greater rate than it appears in the blood. The influences concerned with this storage mechanism will be considered later; at present it is sufficient to quote MacLean's remarks that "as a working rule, if the blood-sugar fails to return to its original level within about 1½ hours after a single 50-grm. dose of glucose, we may consider that a defect in storage is present."

The oxidation of the ingested glucose by the tissues is a small factor in the reduction of the blood-sugar content. Bornstein and Holm (41) have shown that an increase in the respiratory quotient occurs within 30 minutes to one hour of the ingestion of glucose (100 grm.). The increase appears at the point at which the blood-sugar commences to fall, and continues for some time after the initial level has been reached. Sanger and Hun (42) estimate that the sugar oxidized during 2½ hours is only 18 *per cent.* of the ingested carbohydrate (100 grm.), but the metabolic rate is not increased with larger dosage, the CO_2 output being the same for small or large amounts of carbohydrate.

The work of MacLean and his co-workers is in confirmation of that of other investigators in connection with the blood-sugar curve in healthy adults (Baudoin (43), Frank (44), Tachau (45), Jacobsen (46) and Sakaguchi (47)). Of these observers Sakaguchi records details of blood-sugar curves taken at ten-minute intervals in healthy young adults following a 100 grm. sugar meal. In his cases the highest point varied between 0·133 and 0·191 *per cent.* blood-sugar; the rapid fall in concentration after the maximum was reached was constant in all his cases, reaching the original level in 50 to 90 minutes after the meal had been taken. In the work of Hopkins (48), Hamman and Hirschmann (49) and Bailey (50) on the relation of hyperglycæmia and glycosuria, there is substantial evidence that in the normal case the renal threshold for glycuresis is at a blood-sugar level of about 0·17 *per cent.*

There is, however, some alteration in the type of curve with age. Infants under one year of age show a much smaller blood-sugar rise with appropriate sugar dosage; children behave much the same as young adults; but although the maximum blood-sugar concentration may vary from about ·110 to ·210 *per cent.*, *the rapid return to the fasting level within* 90 *minutes* is a constant feature in the healthy young or middle-aged individual.

Spence (38) investigated a series of five apparently healthy men of ages varying from 62–75 years of age, and found four to show high blood-sugar levels and sustained hyperglycæmia two hours after a 50-grm. glucose meal.

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Factors influencing the normal blood-sugar curve.—Labbé and Theodoresco (51) and Jacobsen (46) have recorded that the ingestion of fat causes a diminution in the rise of the blood-sugar curve. This finding, however, has not been confirmed by other workers. Oliver and Haworth (52) have found that ingested fat exerts a decided influence on the blood-sugar curve, and that there is an association between fat and carbohydrate metabolism. Fat in quantity given 4–12 hours before 50 grm. of glucose, or if the sugar is suspended in fat, causes a marked rise and a prolongation of the blood-sugar curve. Excess of fat in the blood, therefore, appears to interfere with glycogenesis. If, however, a large quantity of fat be taken 18–24 hours before the glucose meal, a more rapid fall of blood-sugar is noted. Fat properly absorbed into the tissues appears to increase the storage of carbohydrate, and if not absorbed or mobilized by calcium the storage is inhibited.

The influence of preceding carbohydrate diet is of importance. Lower curves may result in individuals who for some days previous to the test have been on a diet rich in carbohydrate. This fact finds explanation in the work of Foster (53) and Hamman (54), who showed that a second glucose meal does not produce a marked blood-sugar rise, *i.e.*, the glycogenic mechanism is in a state of marked activity. On a preceding non-carbohydrate diet the converse is true, and higher curves may result owing to the previous lack of exercise of the storage mechanism.

For this investigation the cases have been examined after more than a twelve hours' fast, and have been on ordinary hospital diet. In general the question of diet does not enter into the nature of the results obtained.

There is evidence that blood-sugar values may be influenced by surrounding temperature. Warm-blooded animals show an increase of blood-sugar in the cold (Bang (55)), and an increase may also be noted in animals and man in the tropics (de Langen (56)). I am unaware of the exact influence of temperature on the blood-sugar curve, but with the cases examined we are only concerned with room temperature variations.

The state of bodily activity is also of importance: light work may increase and hard labour decrease blood-sugar values (Bang (55) and Bergsma (57)). The cases reported were kept at rest during the experiment.

In this investigation the author has had the opportunity of examining 14 normal cases from laboratory workers and members of the hospital staff. The maximum blood-sugar concentration following a 50-grm. glucose meal varied from 0·15–0·21 *per cent.*, but the rapid return to or below the original ·125 fasting level within 90 minutes to 2 hours was a constant finding. The massed blood-sugar curves are shown in Fig. 1.

Results.

The results obtained in the mental cases will be presented in the following form, the main classification depending on the blood-sugar level two hours after glucose ingestion (50 grm.).

(1) Cases showing blood-sugar curves approximating to the normal type, *i.e.*, maximum blood-sugar level not exceeding 0·2 *per cent.*, with return to the region of the original fasting level in two hours.

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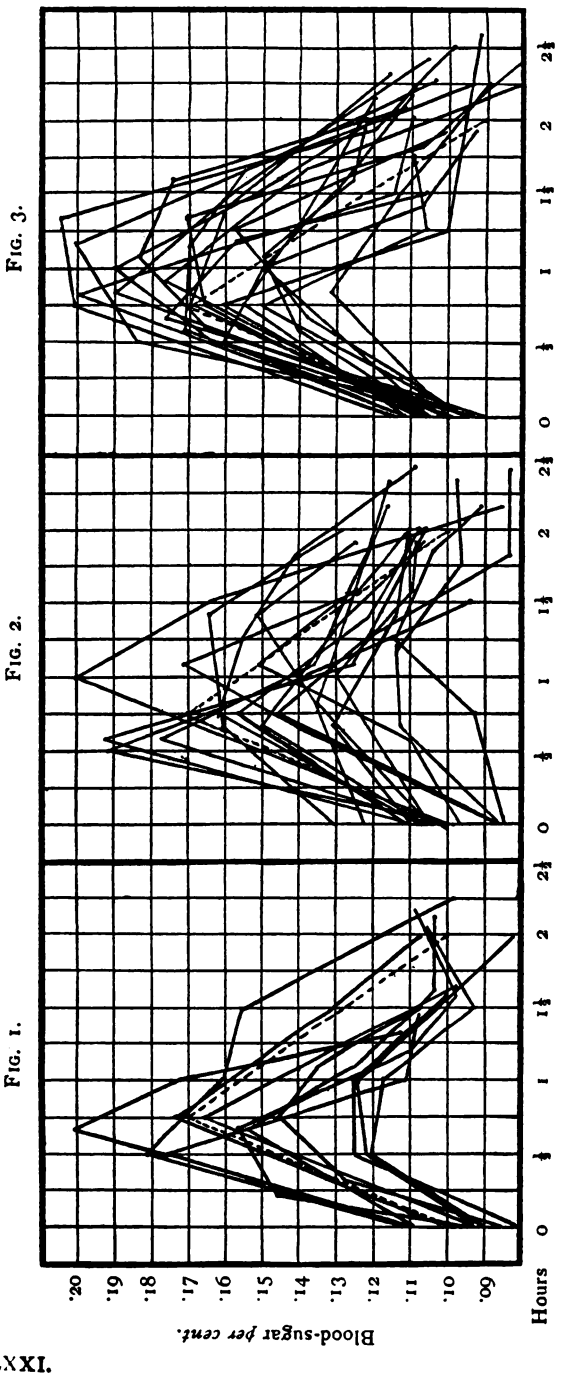


Fig. 1.—Massed blood-sugar curves from fourteen normal individuals. Dotted line: average normal curve.
Fig. 2.—Blood-sugar curves approximating to normal type occurring in early cases of mental disorder (male cases). Dotted line: average normal curve.
Fig. 3.—Blood-sugar curves approximating to normal type occurring in early cases of mental disorder (female cases). Dotted line: average normal curve.

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(2) Cases showing sustained hyperglycæmia with low blood-sugar levels.

(3) Cases showing sustained hyperglycæmia with maximum blood-sugar levels within the normal range.

(4) Cases showing sustained hyperglycæmia with high blood-sugar levels, *i.e.*, maximum values exceeding 0·18 *per cent.*

(1) *Cases with Blood-sugar Curves approximating to the Normal Type.*

Fifty-four patients (20 male, 34 female) fall into this group. They are noted in Table I, and the massed curves shown diagrammatically in Figs. 2 and 3. It will be seen that most mental types are represented in this series of cases; some of them have maintained improvement since their discharge from hospital, others have since been certified. Although the cases show blood-sugar levels approximating to the original fasting value about two hours after glucose ingestion, it will be noted that in general the blood-sugar levels are higher, and there is a tendency to delay before the maximum value is obtained and the storage mechanism sets in, and also a tendency to sustained hyperglycæmia. It is probable that some of these cases would show abnormal curves with increased sugar dosage. A few cases illustrating these tendencies are given (Fig. 4). These cases also illustrate another point of interest; that, although high blood-sugar levels may occur for 1½ hours after the glucose meal, the storage mechanism may set in with marked rapidity, and within 20–30 minutes restore the level to the original fasting value.

TABLE I.

	Males.	Females.		Males.	Females.
Dementia præcox	9	3	Post-encephalitic syndrome	—	2
Melancholia	3	9	Paralysis agitans with depression	—	1
Depression	—	2	Nervous child	1	—
Hypochondria	—	1	Mentally defective	1	—
Anxiety neurosis	3	5	Cretin	—	1
Epilepsy	1	1	Disseminated sclerosis	—	1
Epilepsy with hysteria	—	1	Progressive lenticular degeneration	—	1
Manic-depressive ins.	—	1	Adiposa dystrophia genitalis	1	—
Confusional insanity	—	1	Hysteria	—	1
Obsessional neurosis	1	1			
Paranoia	—	1			
Paraphrenia	—	1			
Totals				20	34

(2) *Cases with Blood-sugar Curves showing sustained Hyperglycæmia Low Levels.*

Eight patients (3 males, 5 females) are included in this series. They are noted in Table II, and their massed curves shown diagrammatically in Fig. 5. This low type of curve has been designated

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as a " hypoglandular curve " by certain observers, probably owing to the fact that some cases of endocrine dysfunction may give blood-sugar curves of this type, but, as will be seen later (p. 459), such curves are by no means the rule in these cases. Moreover, reference to Figs. 1, 2 and 3 will show that they may occur with apparently normal individuals, and with patients whose curves do not show a sustained hyperglycæmia, and in all cases it is necessary to bear in mind the metabolic condition of the individual, for low curves may occur in those prone to diet rich in carbohydrates.

FIG. 4. FIG. 5.

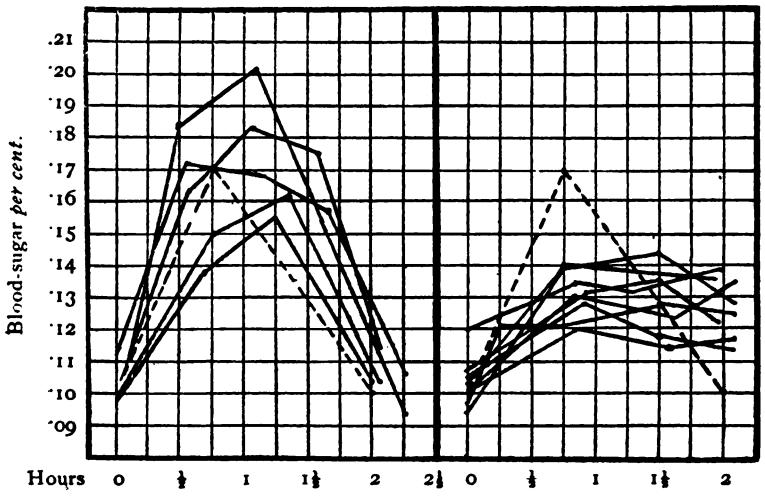


FIG. 4.—Blood-sugar curves approximating to normal type from early cases of mental disorder; showing high and late maximum levels, with rapid glycogenesis. Dotted line: average normal curve.

FIG. 5.—Showing blood-sugar curves of low level with sustained hyperglycæmia (male and female cases). Dotted line: average normal curve.

TABLE II.

	Males.	Females.		Males.	Females.
Paraphrenia . .	—	3	Melancholia . .	1	—
Anxiety neurosis .	1	2	Manic-depressive ins. .	1	—
Totals				3	5

(3) *Cases Showing Sustained Hyperglycæmia amd Maximum Blood-sugar Levels within the Normal Range.*

Forty-one patients (9 males, 32 females) are contained in this group. They are noted in Table III, and represented diagrammatically in Figs. 6 and 7.

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TABLE III.

	Males.	Females.		Males.	Females.
Dementia præcox .	3	2	Epilepsy . . .	—	2
Melancholia . .	—	6	Mania . . .	1	1
Depression .	—	1	Delusional insanity .	—	1
Anxiety neurosis .	1	10	Obsessional neurosis .	1	—
Hysteria . . .	—	4	Chorea . .	—	1
Paraphrenia . .	—	3	Korsakow's syndrome.	1	—
Post-encephalitic syndrome . .	2	1			
Totals				9	32

FIG. 6. FIG. 7.

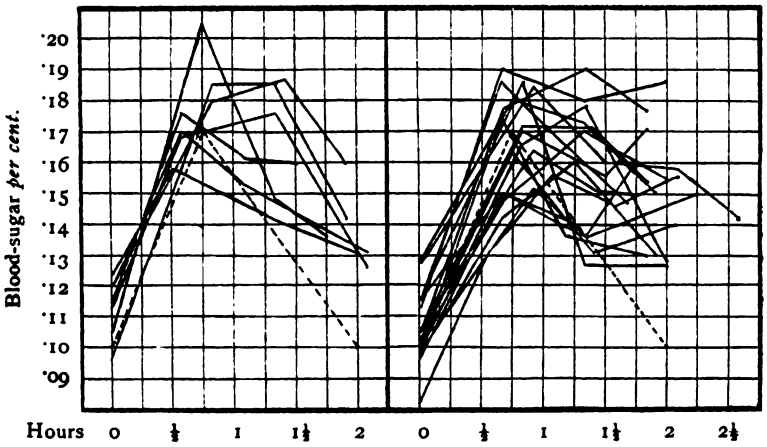


FIG. 6.—Blood-sugar curves of average normal level showing sustained hyperglycæmia (male cases). Dotted line: average normal curve.

FIG. 7.—Blood-sugar curves of average normal level showing sustained hyperglycæmia (female cases). Dotted line: average normal curve.

(4) *Cases showing Sustained Hyperglycæmia with High Blood-sugar Levels.*

Forty-nine patients (13 males, 36 females) are included in this series. They are noted in Table IV, and represented diagrammatically in Figs. 8 and 9.

TABLE IV.

	Males.	Females.		Males.	Females.
Dementia præcox .	1	5	Paraphrenia . .	2	1
Melancholia . .	8	12	Obsessional neurosis .	—	1
Anxiety neurosis .	—	10	Acute confusion. .	1	—
Depression . .	—	1	Hysteria . . .	—	1
Manic-depressive ins. .	—	3	Post-encephalitic syndrome . . .	1	2
Totals				13	36

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Considering Groups 3 and 4, as would be expected there was a greater frequency of glycosuria in Group 4, but in these abnormal cases the blood-sugar level following glucose ingestion may exceed the generally accepted renal threshold value (0·18) and rise to 0·25 *per cent.* or more without glycosuria. In both groups cases of anxiety neurosis and melancholia predominate, but as these cases form the greater part of the admissions to the Maudsley Hospital it is impossible to give comparative figures. It will be

FIG. 8. FIG. 9.

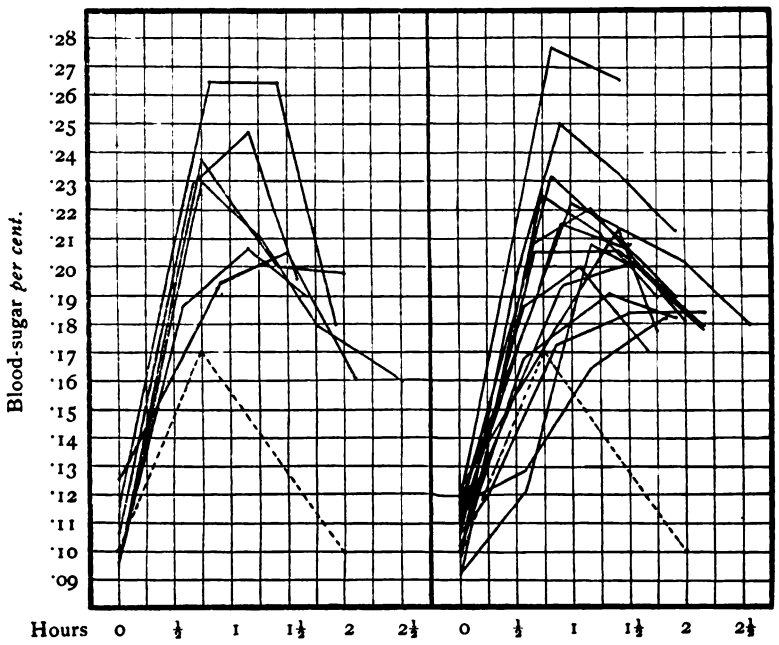


FIG. 8.—Blood-sugar curves of high levels with sustained hyperglycæmia (male cases). Dotted line: average normal curve.

FIG. 9.—Blood-sugar curves of high levels with sustained hyperglycæmia (female cases). Dotted line: average normal curve.

noted that in all the groups all types of cases may occur. In dementia præcox any type of blood-sugar curve may be obtained, from normal to one showing high levels and markedly sustained hyperglycæmia, according to the phase of the mental condition, but it is in the stuporose state that the most marked abnormality is found. In general a blood-sugar curve with sustained hyperglycæmia may occur in any mental condition associated with depression, and it is most marked in acute melancholia and stuporose dementia præcox—Group 4.

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Reference to Figs. 8 and 9 will show types met with in Groups 3 and 4, in which the blood-sugar rise may be normal and the storage delayed, or there may be both delayed rise and fall of the curve.

With regard to the fasting levels in these cases my results do not indicate that there is any marked variation from the normal range, except in very restless cases. I am indebted to Dr. Le Marquand for the following series of fasting levels on consecutive days in three cases of acute psychosis included in the series; consecutive figures of three normals are added for comparison.

Case.	Blood-sugar fasting levels.							
Marked confusion with restlessness	·100	·103	·109	·098	·111	·118	·100	·106
Melancholia with anergia	·095	·106	·095	·110	·093	·100	—	—
Marked melancholia with anergia	·100	·095	·100	·100	·100	·100	·088	—
Normal F.	·100	·100	·103	·093	·093	·109	·103	·106	·112	·112	·116
„ M.	·109	·103	·103	·097	·077	·109	·099	·106	·103	·106	·106
„ F.	·103	·093	·106	·106	·109	·116	·103	·103	·100	·116	·106

Variations in the Abnormal Blood-Sugar Curve.

In certain recoverable cases there is evidence to show that the blood-sugar curve may be taken as an index of the progress of the case, for with improvement the curve tends to become more normal in character, and on recovery may conform to the normal type. From a number of such cases the following are illustrative examples: Fig. 10, showing difference in curve after one month in hospital; Fig. 11, showing curve on admission, on recovery and discharge and four months later; and Fig. 12, showing curve on admission, one month later and on recovery and discharge.

There may also be a change with alteration in mental condition. Fig. 13 illustrates the curves obtained in the stuporose and excited states of a manic-depressive case.

The variations in the blood-sugar curve may also determine the value of treatment. Blood-sugar curves before and after treatment were obtained in eight cases that were on thyroid (5 gr. *per diem*) for one month; the clinical improvement or otherwise was coincident with the variation in the blood-sugar curve. Of these cases Figs. 14 and 15 are illustrative of the beneficial and adverse effect of the thyroid therapy.

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FIG. 10. FIG. 11.

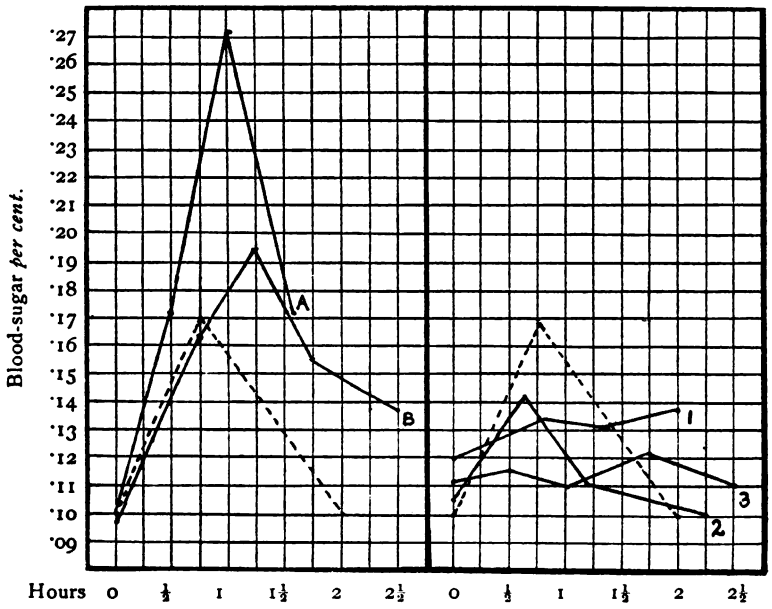


FIG. 10.—Acute melancholia. A. Blood-sugar curve soon after admission. B. Blood-sugar curve one month later.

FIG. 11.—Anxiety and depression. Blood-sugar curves (1) on admission; (2) on recovery and discharge; (3) four months later, slight relapse.

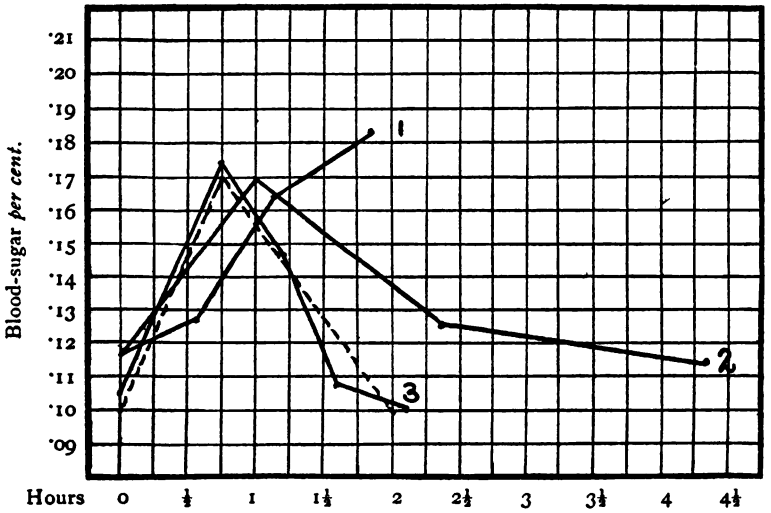


FIG. 12.—Melancholia. Blood-sugar curves (1) on admission; (2) one month later; (3) on recovery and discharge.

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Blood-Sugar Curves in Mental Disorders.

Using a standardized glucose meal of 1·75 grm. glucose per kilo body-weight followed by blood-sugar determination at hourly periods, Olmsted and Gay (58) have investigated a series of cases including types of mental disorder. In hysteria 75 *per cent.* of uncomplicated cases gave normal curves, but with manic-depressive insanity they found variable but high levels after one hour with sustained hyperglycæmia. Drury and Farren Ridge (59), using the same technique as adopted in this laboratory, record the results in 100 insane cases. In epilepsy the blood-sugar curves approximated closely to the normal. Cases of general paralysis, confusional insanity, manic-depressive psychosis, dementia præcox and climacteric psychoses were investigated and showed varying abnormal sugar curves in a good number of the cases. The authors conclude that, amongst the mental symptoms,

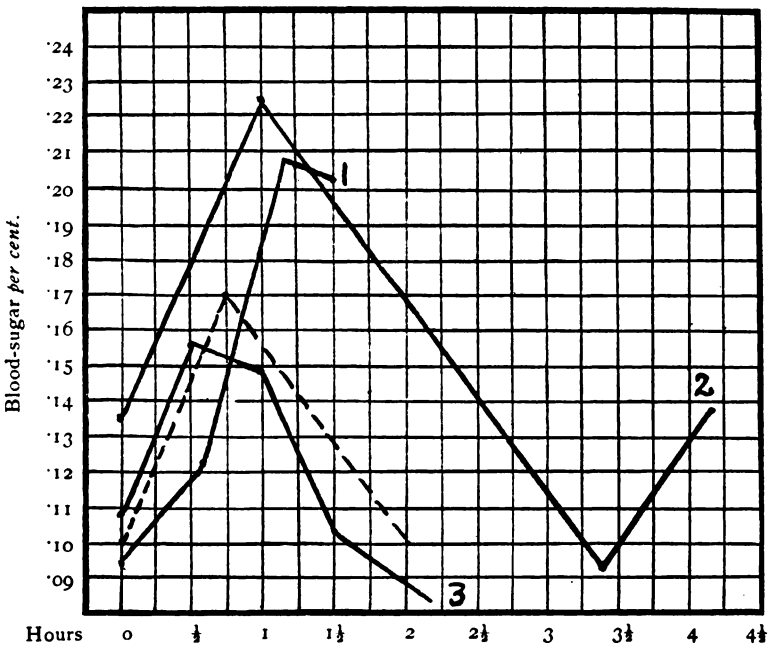


FIG. 13.—Manic-depressive insanity. Blood-sugar curves (1) and (2), depression, stupor; (3) mania.

confusion and melancholia are associated with the greatest disturbance of the sugar metabolism. Holmström (60), investigating the blood-sugar in epilepsy, reports normal values and normal carbohydrate tolerance, and concludes that observed variations have no primary significance. Other investigations have been recorded by Tsuchiya (61) and Schryver (62); their technique being different, the results are not comparable with mine, but they agree in the main fact that in psychoses there is evidence of disordered carbohydrate metabolism. Lorenz (63), investigating the sugar tolerance in dementia præcox and other mental disorders, reports the occurrence of normal fasting levels except in cases of active catatonia, and cases in which evident emotional upsets existed at the time of the test. Patients in the active stages of catatonic dementia præcox gave blood-sugar curves resembling hyperthyroidism; the curves of simple deteriorating dementia præcox resembled those obtained in certain endocrine disturbances, such as dyspituitarism; and the curves of manic-depressive cases (depressed phase) were higher than those found in normal subjects.

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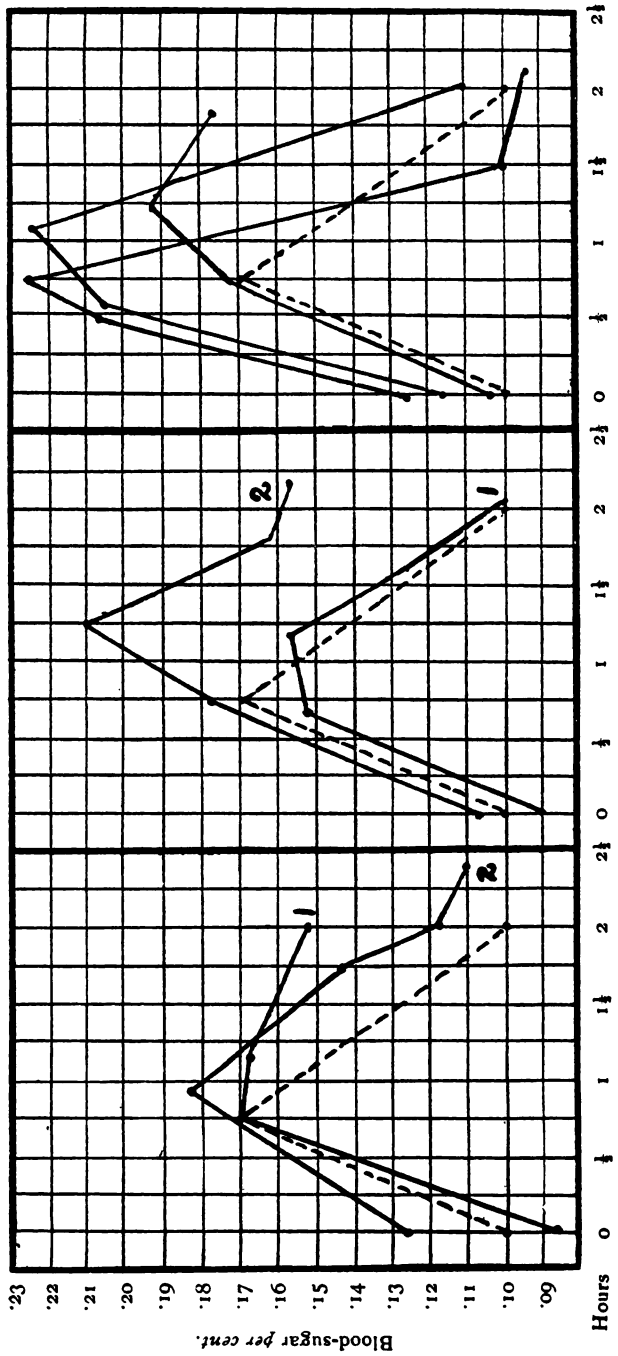


FIG. 14. FIG. 15. FIG. 16.

FIG. 14.—Anxiety and depression. Blood-sugar curves (1) before and (2) after thyroid therapy for one month. Condition improved.
FIG. 15.—Melancholia. Blood-sugar curves (1) before and (2) after thyroid therapy for one month. Condition worse.
FIG. 16.—Hyperthyroidism. Blood-sugar curves after 50 grm. glucose meal. Glycosuria. Dotted line: average normal curve.

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Blood-Sugar Curve Variations in Disease and other Abnormal Conditions.

Infective conditions.—An abnormal sustained hyperglycæmia following glucose ingestion may occur in various infective conditions.

Olmsted and Gay (58) show sustained curves in a number of cases of focal infection. Pemberton and Foster (64), investigating chronic arthritis, obtained curves showing sustained hyperglycæmia in severe cases, but normal curves were obtained following removal of the septic focus (teeth or tonsils).

Staveley Dick (65) reports hyperglycæmia and high and prolonged blood-sugar curves following glucose administration, after vaccine injection in non-diabetic cases. He would explain this as a defensive hyperglycæmia, but Allen (66), in his comments on these results, regards them as due to toxic depression of pancreatic function. In this connection it is of interest to mention that Rosenthal (67) showed that the injection of diphtheria toxin prevented glycogen formation.

Sustained blood-sugar curves may be found in nephritis (Tachau (45), Bailey (50), Hopkins (48) and Hamman and Hirschman (49)), and in carcinoma (Olmsted and Gay (58), Fredenwald and Grove (68), and Rohdenberg, Bernard and Krehbiel (69)), but there is no characteristic type of curve in these diseases.

In the endeavour to arrive at an explanation of these abnormal findings and their significance, it is necessary to consider the known influences regulating carbohydrate metabolism as expressed by the blood-sugar curve. In mental disorders we are concerned (1) with alteration of blood-sugar regulation in emotional states, and (2) with variations from the normal response to a sugar meal. Following the course of the blood-sugar curve our main attention is drawn to the influences governing absorption and storage—glycogenolysis and glycogenesis, the other factors, combustion and excretion, being of minor importance in the fall of the curve.

For this purpose the following influences will be considered in relation to the blood-sugar curve :

1. The endocrines.
2. The diastatic power of the blood.
3. The influence of the sympathetico- and parasympathetico-mimetic drugs.
4. The influence of acids and alkalies.
5. The glycogenic function of the liver.
6. Absorption.

The endocrine glands are intimately associated with carbohydrate metabolism, and very speculative hypotheses have been advanced from blood-sugar curves regarding specific endocrine function. The balance of endocrine function, and carbohydrate metabolism, are both extremely complex and at present not clearly understood, and these hypotheses are based more on imagination than on actual fact. Certain types of blood-sugar curves are associated with various diseases of the endocrines, but their frequency is by no means a constant feature; also the blood-sugar curve shows a response to endocrine therapy. A brief survey of these facts,

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however, will be of interest and helpful in our consideration of the changes found in mental states.

The thyroid and parathyroids.—Fig. 16 represents the blood-sugar curves obtained in three cases of definite hyperthyroidism occurring in the present series. They show the usual characters of hyperthyroid curves, *i.e.*, a fasting level slightly raised or within normal limits, and an ascending curve showing high values; the descent to the original level may be normal, or there may be a sustained hyperglycæmia (Olmsted and Gay (58)) denoting defective storage. The thyroid effect appears to be shown in rapid absorption, increased oxidation and diminished tolerance with glycosuria. Cramer and Kruse (70) have shown that thyroid feeding in animals depletes the liver of glycogen, raises the blood-sugar, diminishes sugar tolerance and raises the respiratory quotient. Sanger and Hun (42) record that in hyperthyroidism ingested glucose may be oxidized at twice the normal rate. Excessive thyroid feeding may induce a blood-sugar curve showing sustained hyperglycæmia.

In hypothyroidism variable blood-sugar curves may occur. In myxœdema low value curves, or high values similar to the hyperthyroid type, may follow glucose ingestion, but the tolerance is generally increased. With cretins low curves and an increased tolerance are stated to be a constant finding. Fig. 17 shows a case of myxœdema with blood-sugar curve of the hyperthyroid type; it is of interest that at first there was no glycosuria with the carbohydrate meal, but following thyroid therapy the tolerance was lowered and glycosuria resulted.

The removal of the parathyroid in experimental animals leads to a reduction of sugar tolerance and to a high blood-sugar curve after glucose administration (Underhill and Hilditch, etc. (71) (72)).

The pituitary.—There is evidence to show that the pituitary is concerned with blood-sugar regulation, and its action is antagonistic to the influence of insulin; injection of the anterior lobe is without effect, whereas the posterior lobe causes hyperglycæmia.

The blood-sugar curve in acromegaly is characterized by a high fasting level, high maximum level and a fairly rapid return to the original level, with glycosuria.

In cases of hypopituitarism the blood-sugar curve may be variable; it is the rule for curves of low sugar values to occur. Calvert and Langmead (73), investigating obesity in children, were unable to report any characteristic form of blood-sugar curve in cases of reputed dyspituitarism; they deviated from the normal to a greater or less degree, and presented other variable features. Their work on the influence of endocrine extracts on these blood-sugar curves might be construed as indicating that a properly balanced

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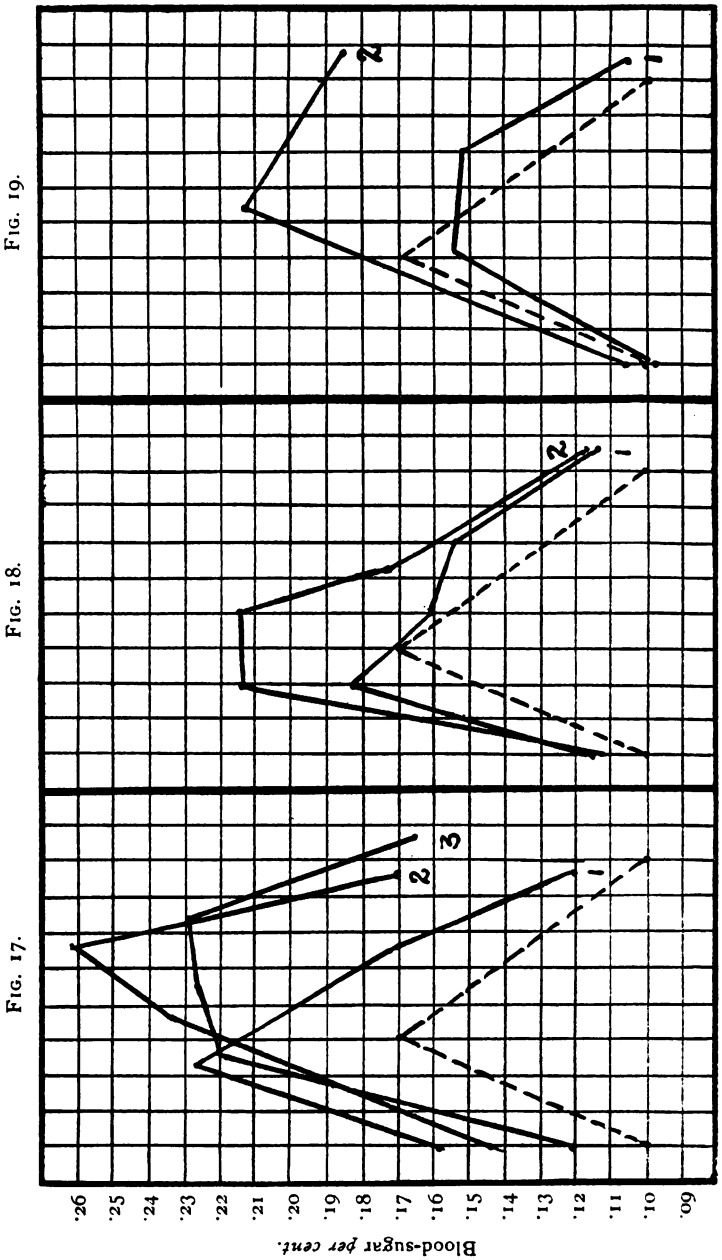


FIG. 17. FIG. 18. FIG. 19.

FIG. 17.—Hypothyroidism; melancholia. (1) Blood-sugar curve; (2) and (3) after thyroid therapy, with glycosuria. Dotted line: average normal curve.

FIG. 18.—Normal. (1) blood-sugar curve after 50 grm. glucose; (2) blood-sugar curve after 50 grm. glucose and adrenalin subcutaneous injection (5 mns. 1–1,000).

FIG. 19.—Post-encephalitic syndrome. (1) Blood-sugar curve after 50 grm. glucose; (2) blood-sugar curve after 50 grm. glucose,

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pluriglandular therapy is required, and that the production of a normal blood-sugar curve may prove a useful guide to treatment.

The adrenals.—The blood-sugar rise following adrenalin injection will be considered later (p. 464). An excess of adrenalin causes glycogenolysis and hyperglycæmia. This action, however, appears to be dependent on thyroid co-operation, for if thyroidectomy is performed previous to the adrenalin injection, the adrenalin is either inactive or much larger dosage is required (Eppinger (74)).

Emotional hyperglycæmia and glycosuria are believed to be due to the same mechanism as the hyperglycæmia and glycosuria following Bernard's *piqûre* of the floor of the fourth ventricle, *i.e.*, splanchnic stimulation to the suprarenals causing hypersecretion of adrenalin and mobilization of the liver glycogen. The effect of adrenalin on the blood-sugar curve is shown in Figs. 18 and 19. In the normal case the blood-sugar rise is rapid, with high values, but the fasting level is reached within the usual two hours; the mental case, however, shows a sustained hyperglycæmia.

The pancreas.—It has long been recognized that the pancreas is essential for glycogenesis, and that dysfunction of that organ results in hyperglycæmia and glycosuria, and the characteristic blood-sugar curve showing prolonged hyperglycæmia. The action of insulin on the blood-sugar curve is too well known to need further mention. The discovery of insulin, however, has enabled more exact information to be gleaned regarding the *rôle* of the pancreas, in particular the islets of Langerhans, in carbohydrate metabolism (MacLeod (75)). The action of insulin is enzyme in type, *i.e.*, when the substrate is small in proportion to the amount of enzyme, the increasing amount of substrate acted upon becomes less and less, the reaction proceeding according to a logarithmic equation. Its action is concerned with glycogenesis and carbohydrate utilization. The glycogen content of the liver of depancreatized dogs fed with sugar shows a marked increase after insulin injection, and there is also a rise in the respiratory quotient. The blood and liver fat are diminished in amount (*cf.* p. 448). With the blood-sugar curve the pancreatic action is seen in the sudden fall of the blood-sugar values, and its action is apparently decided by the blood-sugar concentration, for when the maximum level is reached—generally about 45 minutes after the sugar has been administered—there is a rise in the respiratory quotient (Bornstein and Holm (41)) and rapid glycogenesis ensues. In cases of mental disorder this pancreatic reaction may be delayed or determined only at higher blood-sugar levels.

It is evident, then, that excessive activity of the thyroid, suprarenals and pituitary (posterior lobe) results in a blood-sugar rise

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and diminished sugar tolerance, that adrenalin causes glycogenolysis, and may inhibit glycogen formation, and also that the storage effect (glycogenesis) shown by the fall of the blood-sugar curve is induced by the action of the pancreas.

The mechanism by which these influences effect blood-sugar regulation is unknown, but the work of Langfeldt (76) on the action of endocrine secretions on the glycolytic power of liver diastase is of considerable interest in this direction. He has shown *in vitro* that thyroxin alone has no effect on the hydrolysis of glycogen by liver diastase, but adrenalin so diluted that it has no effect becomes very active when thyroxin is added. Langfeldt considers blood-sugar regulation to be dependent upon the pH of the liver, and, as the result of his experiments and observations, puts forward the following theories regarding the mechanism whereby hyperglycæmias may arise :

(1) By the change of the hydrogen ion concentration of the liver tissue.

Under normal conditions practically only the phosphate and chloride diastase are of importance, and of these the chloride diastase is more important on account of the greater affinity of the Cl ion for diastase. The optimum of the chloride diastase lies at pH 6·8. This hydrogen ion concentration represents neutral reaction at 37° C. Therefore to obtain maximum glycogenolysis the *milieu* of the diastase must be neutral. The action on the blood-sugar concentration of acids given *per os* or by transfusion of the liver, the influence of the gastric juice in depancreatized dogs and the *post-mortem* glycogenolysis are thus explained.

(2) By the displacement of the optimum of the liver diastase to or close to the pH of the liver-tissue.

Such a displacement takes places under the influence of adrenalin, or in a higher degree by the simultaneous effect of adrenalin and thyroidine. It may be that the diastase forms a complex compound with these substances, as it does with phosphates, chlorides and many other substances, and that the affinity between diastase and adrenalin-thyroidine extract is greater than that between diastase and the chloride ion. The new complex compound has its optimum at pH 7·73. The glycogenolysis is very intensive, and even at pH 7·33 is just as heavy as the Cl-diastase at pH 6·8.

(3) By the lack of re-formation of glycogen, such as very probably takes place in pancreatic diabetes, to which diabetes mellitus is due.

Langfeldt's results seemed to indicate a line of investigation that would lead to an explanation of the abnormal blood-sugar curves found in mental disorders. We are concerned with a sustained

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hyperglycæmia, which, in the light of the facts already mentioned, may be due to (1) inhibition of glycogenesis arising from endocrine hyperactivity, (2) excessive diastase activity due to the same cause, or shift of the pH of the liver, and lastly (3) to pancreatic dysfunction.

The shift of the optimum for liver diastase to the alkaline side, (pH 7·73) under the influence of thyroxin and adrenalin, gave promise of a method whereby one might possibly determine the presence of thyroid reacting bodies in the serum, by testing its activating properties on the glycolytic action of liver diastase in the presence of dilute adrenalin solution at a pH of 7·73. Or, by testing the activating properties of various sera on the glycolytic power of liver diastase at selected hydrogen ion concentrations, it might be possible to detect the activating influence of thyroid-adrenalin reacting bodies. Attempts were made in this direction, but without success, owing (1) to the fact that it was impossible to destroy the more active diastatic action of the serum which masked all other reaction, and (2) to the fact that serum inhibits adrenalin action (Stewart) (102).

It was considered advisable, however, to examine the diastatic power of the blood in a number of cases, and to investigate whether any variation in diastatic activity could be discerned as the result of endocrine administration. It may be stated at once that the results throughout were of a negative character, and will receive but brief mention.

Investigation of the diastatic action of the blood.—The determination of the blood diastatic power has been made by digesting starch solution with 0·2 c.c. of blood at 37° C., and estimating the sugar production after 20, 40 and 60 minutes. Glycogen has also been used as substrate and the reaction estimated by sugar determinations, or by colorimetric estimation of the glycogen remaining at varying periods up to 20 hours. There is a fallacy regarding the estimation of the end-product as an index of the reaction in that intermediate products may occur, and attempts were made, though unsuccessful, to adopt the more satisfactory method and estimate the diminution of substrate by nephelometric methods.

The activity of diastase varies with the pH of the medium in which it acts, and this optimum is different according to the salt content of the medium (Michaelis and Pechstein (77) and Norris (78)). The optimum in the presence of phosphates is at pH 6·2, and in the presence of chlorides pH 6·7.

To avoid errors due to a varying medium the substrates used were buffered with Sorensen's solutions to pH 6·2. The actual substrate used was equal parts of 0·4 *per cent.* soluble starch solution and Sorensen's phosphate buffer solution of pH 6·2. Four 0·2 c.c.

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specimens of blood were taken from the subject from a finger-prick, and each added to 1·8 c.c. of the starch substrate. The sugar content of one specimen was determined at once, and the remaining specimens heated in a water-bath at 37° C., and sugar estimations made after 20, 40 and 60 minutes. A series of 12 normals and 12 patients suffering with varying types of mental disorder were examined. The results were by no means constant, variations occurring with the same case on different days, and the range of this inconstancy was the same for both normals and patients. As far as could be judged there was no increased glycogen or starch-splitting power as a response to adrenalin ($\frac{1}{8}$ c.c. 1–1000) injection, to thyroid feeding and injection, or as a result of vigorous exercise. The same type of results was obtained repeating the tests but using glycogen solution buffered to pH 6·2 as substrate, and estimating the reaction by the disappearance of substrate, *i.e.*, glycogen by colorimetric determination. The one case that gave results well out of the range of the variations in the normal and other subjects was a diabetic included in the series of patients.

A further experiment was made to test the activity of blood diastase before and after prolonged thyroid feeding. In this instance the tests were made with a substrate of glycogen solution buffered to a range of hydrogen concentrations from 6·2 to 8·04, and the reaction estimated both by sugar determinations at varying periods and by colorimetric estimations to ascertain the rate of disappearance of the substrate. Again the results were inconstant, but generally they did not indicate an increased diastatic activity as the result of thyroid therapy.

These experiments well demonstrated the known fact of the marked variation of the activity of diastase with ionic change of the medium. Owing to this and other reasons related to changes that may occur within the blood itself, the available methods for the determination of the starch and glycogen-splitting properties of blood attributed to diastase can only be regarded with suspicion, and the general conclusion that the amount of diastase in the blood does not suffer variation under the conditions of the experiments requires further support than that of the results of diastase tests at our disposal. It may be mentioned, however, that the tests were made on exactly comparable lines, and the general conclusions receive support from the work of MacLeod (79).

Sympathetic and parasympathetic glycæmia.—In view of the close association of the autonomic nervous system with carbohydrate metabolism and blood-sugar regulation, it was deemed of interest to investigate the comparative response of a series of mental cases and normal controls to the subcutaneous injection of

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sympathetico-mimetic and parasympathetico-mimetic drugs, adrenalin and pilocarpine, by variations in fasting blood-sugar values, and blood-sugar curves after glucose ingestion.

Variation in fasting blood-sugar levels following pilocarpine injection, $\frac{1}{20}$ gr.—Altogether 16 cases, 3 normals and 13 patients, were examined, blood-sugar determinations being made at varying intervals for one to two hours after pilocarpine subcutaneous injection. The results were negative in every case; no variation in the blood-sugar levels could be observed.

Variation in fasting blood-sugar levels following adrenalin injection.—In 5 normal cases examined there was no blood-sugar rise following the injection of 2 minims (1–1000) adrenalin solution. Following the subcutaneous injection of 5 minims (1–1000) adrenalin solution all cases examined showed a variable blood-sugar rise. Sixteen patients and 5 normal controls were investigated; the maximum blood-sugar values ranged up to 0·15 *per cent.*, and the same variations occurred in the normals as in the patients examined. Nothing could be ascertained regarding the respective blood-sugar response to adrenalin in various types of mental disorder, and it is evident that any attempt to estimate individual sensitiveness to adrenalin stimulation as indicated by the blood-sugar response must be made by determining the dosage necessary to produce a given response rather than the effect produced by a given dosage.

Comparison of variations in fasting blood-sugar levels following adrenalin stimulation, preceded by pilocarpine injection.—Eleven patients (8 females and 3 males) and 1 normal were investigated for the blood-sugar response to the subcutaneous injection of 5 minims of adrenalin solution. On another day the blood-sugar response was ascertained for the same adrenalin dosage one hour after the subcutaneous injection of $\frac{1}{20}$ gr. pilocarpine.

The normal showed a slight depression of the adrenalin effect following pilocarpine as judged by blood-sugar rise; all the mental cases gave a similar reaction with the exception of two, and in these the slightly increased adrenalin effect could not be associated with any feature of the cases.

The influence of sympathetico-mimetic and parasympathetico-mimetic drugs on the blood-sugar curve.—A series of tests have been made to investigate the variations in the blood-sugar curve following glucose ingestion, with the subcutaneous injection of adrenalin, with pilocarpine $\frac{1}{20}$ gr., and with atropine $\frac{1}{100}$ gr.

The adrenalin effect is shown by a sharp rise in the blood-sugar curve; the return to the original level may occur in normal time or the hyperglycæmia may be sustained. The pilocarpine reaction may be in the form of a depression of the blood-sugar curve, or the

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blood-sugar curve may be depressed at first, but followed by a marked rise. The action of atropine is to reduce the levels of the blood-sugar curve.

It is again necessary to emphasize that the action of sympathetico- and parasympathetico-mimetic drugs depends on respective dosage; reference to the work of Bertram (80) shows a hyperglycæmia in response to adequate pilocarpine dosage; also simultaneous injection of pilocarpine with adrenalin abolishes the adrenalin hyperglycæmia. Also the work of Schenk and Heimann-Trosien (81) in the case of adrenalin would appear to indicate that the response may be merely an expression of the rate of absorption.

The Influence of Acid and Alkali on Carbohydrate Metabolism.

In view of the well-known influence of hydrogen ion concentration on enzyme action in general, it is not surprising that the administration of acid and alkali will markedly alter both glycogenolytic and glycogenetic processes. The effect of acids on the metabolism of carbohydrates was investigated by Elias (82), (83), (84) and his co-workers. They observed that small amounts of acid by mouth (rabbits and dogs), as well as by transfusion of the liver (turtles), caused glycogenolysis, with subsequent hyperglycæmia and glycosuria.

The work of Haldane (85) on experimental and therapeutic alterations of human tissue alkalinity is of considerable interest in this direction. Sodium bicarbonate in massive doses is rapidly excreted, but it is possible to increase the blood alkali reserve by 20 *per cent.*, and the alveolar CO_2 rises in about the same proportion owing to slowing of respiration. The reaction of the arterial blood is little altered, although doubtless the liver becomes very alkaline. Alkalosis, whether due to over-breathing or alkali ingestion, causes a disturbance of carbohydrate metabolism like that of diabetes. Aceto-acetic acid and β oxybutyric acids appear in the urine. The respiratory quotient falls to 0·70 and lower. The fasting blood level rises slightly, but polarimetric examination by the method of Winter and Smith (p. 468) shows that, as in diabetes, the normal sugar has been replaced by a highly dextro-rotatory substance. Five hours after 60 grm. of $NaHCO_3$ a normal glucose tolerance of 200 grm. is reduced, and 100 grm. gave a blood-sugar curve rising to 0·19 *per cent.* with sustained hyperglycæmia without abolishing the acetonuria.

Haldane, from his results, points out that it may be inadvisable to push alkali treatment too far, and quotes Aldersberg (86), who induced acidosis in mild diabetics by daily doses of 18 grm. $NH_4H_2PO_4$, and was able thereby to halve the acetone excretion and in some cases the glucose excretion also. His results may be due to increase in blood phosphates, but the probability remains that glucose is best oxidized on the acid side of the normal reaction. When, however, the acidosis is pressed too far a different type of carbohydrate metabolism occurs. The respiratory quotient is normal or high, indicating oxidation of carbohydrates. The rotating power

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of blood-sugar and the fasting level are normal. One hundred grm. of glucose produce a blood-sugar rise to 0·19 *per cent.* with glycosuria. There is a failure to store glucose, but not to oxidize it.

Results on the influence of acid and alkali, introduced by intravenous injection, on the blood-sugar curve following glucose ingestion in animals are recorded by Bertram (87); in his experiments acid produces a sharp rise in the curve with a tendency to hyperglycæmia, whereas alkali causes no apparent rise but a slight sustained hyperglycæmia; there is an increase in adrenalin hyperglycæmia when acid is injected simultaneously.

From the results I have obtained it is evident that the effect of acid and akali *per os* on the blood-sugar curve depends on dosage, the type of acid and alkali administered, and the time in relation to the sugar meal when they are administered. The question has some importance from a therapeutic point of view, and the results will be reported in a later communication. There is, however, a marked variation in carbohydrate metabolism as the result of acid and alkali ingestion.

While considering the influence of ionic change, it is of interest to note that Underhill and Closson (88) induced a hypoglycæmia with glycosuria and diuresis following intravenous injection of sodium chloride, and this reaction could be counteracted by subsequent injection of saline solutions containing calcium chloride.

The Glycogenic Function of the Liver.

In a number of cases in which the blood-sugar curve is recorded, the lævulose test for liver glycogenic efficiency was also made. The results of the latter investigation are reported in detail (p. 474), and here it is only necessary to note that the results *were negative in 21 cases*, two cases only giving results of a positive character. Twenty-three cases were thus examined, 9 of which gave normal curves, and 12 abnormal blood-sugar curves showing sustained hyperglycæmia after glucose ingestion. The 2 cases positive to the lævulose test gave normal glucose curves.

The cases examined were: *With normal blood-sugar curve, males*, 3 cases; *females*, 8 cases.[1]

With blood-sugar curves showing sustained hyperglycæmia: Low level, male, 1 case; *female*, 1 case. *Normal level, male* 1 case; *females*, 3 cases. *High level, females*, 7 cases.

The results indicate that if the lævulose test gives a true indication of the glycogenic function of the liver, there is no impairment of function in mental cases giving all types of blood-sugar curves, normal and abnormal, after glucose ingestion.

[1] Lævulose test, positive (?), 2 cases.

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Absorption.

The work of Hewitt (89), (90), (91) and his collaborators on the permeability of the living intestines to various carbohydrates led to the discovery that after contact with the intestinal mucosa optical changes indicated the partial conversion of the stable α and β isomerides of glucose, fructose and galactose into the highly reactive γ modifications. Further work on the relative rates of absorption of δ glucose, δ fructose and δ galactose, from the small intestine, showed that with the normal intestinal wall the absorption rate is in the order glucose, galactose and lævulose; with the epithelial lining destroyed absorption still occurs, but at an equal rate for all three sugars. Attention is also drawn to the influence of calcium and sodium salts on the permeability of cells to these crystalloids.

Concerning the nature of sugar in blood, Winter and Smith (92) have deduced from polarimetric investigation that the sugar in normal blood is the highly reactive γ glucose, while in cases of severe diabetes the blood-sugar is in the stable α and β form.

Winter and Smith (93) have published further work confirming these results and findings on the blood-sugar in diabetics treated with insulin, from which they surmise that insulin induces a greater proportion of the normal γ form. In another communication (94) they have investigated the blood-sugar in adrenalin hyperglycæmia, in which condition the blood-sugar appears to be the same as in the diabetic.

The findings of Hewitt and his co-workers have not received confirmation by the work of Stiven and Reid (95) and Hume and Denis (96). The latter investigators could not agree with the negative results of Stiven and Reid, as, although half their experiments gave negative results, the others gave unmistakable evidence of the existence of a muta-rotation, which, however, they could not ascribe to the transitory formation of γ glucose.

Visscher (97), repeating the work of Winter and Smith, was able to corroborate their observations concerning normal blood, but found that the differences between normal and diabetic blood could be obtained by variation of the pH of the deproteinized blood extract. Denis and Hume (98) could not confirm this statement by Visscher, and also from their results deemed it unjustifiable to consider that the experiments of Winter and Smith furnished proof of the existence of γ glucose in normal blood.

The varied opinions render the evidence concerning the existence of γ glucose unconvincing, but it would seem possible that the sugar that is absorbed and stored in the organism is not the usual α and β

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glucose, but a reactive modification, which, in view of the different behaviour of the monosaccharides, is more readily formed from lævulose.

Hewitt has found that under experimental conditions glucose is absorbed from the gut more rapidly than lævulose, but in practice it is found that absorption may vary considerably in different individuals. In the consideration of the blood-sugar curve following glucose ingestion this does not appear to be a factor of any great importance, because the amount of glucose necessary to be absorbed to cause the onset of the storage reaction is small. Moreover, examination of the blood-sugar curves obtained in this series of cases does not indicate that variations in the absorption rate introduce any abnormality of note.

Discussion and Summary.

The general finding expressed here, that in a large proportion of early and chronic mental cases there is a disordered carbohydrate metabolism as shown by a sustained hyperglycæmia following glucose ingestion, is agreed with by all investigators who have studied the subject. Also this abnormality cannot be associated in particular with any mental condition, but it is generally accepted that its frequency is greater in those associated with melancholia and especially stupor. Various explanations for the abnormal sugar curve have been suggested. Tsuchaya (103) assumes that the hyperglycæmia results from a diminished capacity in the body to burn sugar. It is possible that there may be diminished oxidation in some cases, but all the evidence tends to show that the loss by combustion is a minor factor in the fall of the sugar curve. Schryver (104) offers possible reasons for the abnormality; no definite physical causes are evident, nor emotional states; some suggest onset of diabetes, but probably there is no single reason for several abnormalities, such as those of the thyroid, suprarenal and pituitary glands, and he suggests that liver function would be worthy of investigation. My results from the investigation of the hepatic glycogenic function tend to absolve the liver from blame in this direction. Both authors suggest thyroid, suprarenal and pituitary abnormalities, and Olmsted and Gay (58) point to the similarity of the manic-depressive blood-sugar curves with those of hyperthyroidism. The curves in both conditions are very diverse in character, and the comparison is difficult. I have examined a large number of blood-sugar curves from cases of mental disorder, and, with the exception of those in which the condition is accompanied by obvious endocrine disease, I am unable to classify them in terms of specific endocrine activity, and I

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consider there is a tendency to exaggerate the importance of these glands in seeking for an explanation for the disordered sugar metabolism.

I have endeavoured to consider all the possible factors concerned with the rise and fall of the blood-sugar curve, absorption and glycogenolysis associated with the rise, and glycogenesis, combustion and excretion with the fall.

The results of the liver function tests appear to indicate that the glycogenic function in these cases is not impaired. Lævulose is a good glycogen former, and its glycogen formation takes place mainly in the liver (p. 476). Moreover, apparently this formation can take place independently of pancreatic aid, for lævulose can cause glycogen formation in the livers of depancreatized dogs (de Wesselow (99)). On the other hand, the pancreas is essential for glycogenesis following glucose ingestion. It would appear, then, that in the cases showing sustained hyperglycæmia there is no hepatic inefficiency, and the cause of the hyperglycæmia may be defective pancreatic reaction.

Regarding the question from the point of nervous control, it may be concluded that in the entire absence of adrenalin from the blood it is impossible to excite hyperglycogenolysis by stimulation of the nerve supply to the liver (*piqûre*, splanchnic stimulation, hepatic nerve stimulation) (MacLeod (79)). It is probable that both thyroxin and adrenalin are able to increase glycogenolysis and to inhibit glycogen formation; this is not evident in these cases following lævulose ingestion. Moreover, experimental adrenalin hyperglycæmias following reasonable dosage are not of great magnitude, and emotional hyperglycæmias of the same mechanism still less, and it would seem that this factor does not contribute much to the sustained hyperglycæmia following glucose ingestion in the majority of the cases examined. The adrenalin effect is probably seen more on the lowering of the renal threshold and glycosuria, owing to increased permeability of the tissues; for the explanation of such changes I would refer to the illuminating lectures by Hamburger (100) on the increasing significance of permeability problems for the biological and medical sciences. It is noteworthy that the sustained hyperglycæmia curves tend to show high and late maximum values, and, with a 50-grm. glucose meal, although the maximum values often exceed the accepted renal threshold for glucose, glycosuria is infrequent.

Viewed from the point of view of hormone control, we have to consider two independent vital processes—glycogenolysis and glycogenesis. With both reactions of enzyme-like character there is no evidence to indicate deficiency of the hormones concerned,

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but there is every indication of the extreme sensitiveness of these reactions to change in ionic state of the environment in which they operate. I would refer to the marked effect on their action of changes in the hydrogen ion concentration and salt content, and the disturbance in carbohydrate metabolism from the same causes in animal experiments, etc. Unlike the diabetic, the fasting levels in cases showing markedly sustained hyperglycæmia are generally normal, high values in mental conditions being associated with motor restlessness. The reaction governing the storage mechanism is merely delayed. The pancreas is concerned with glycogenesis represented by the fall of the blood-sugar curve, and in the light of the preceding remarks, it seems reasonable to infer that the cause of the sustained hyperglycæmia in the majority of mental cases showing a defective storage mechanism may be depression of pancreatic function, probably induced by change in the ionic state of the organism. The cases examined in this investigation are early recoverable uncertified cases of mental disorder; but the investigations of Lovell (101) would indicate that this functional inactivity may eventually lead to permanent damage of the pancreas. The blood-sugar curves in infective conditions and following the injection of toxins are very significant, and suggest the possibility of a toxæmic cause for the altered metabolism in these cases, especially intestinal toxæmias.

It may be asked, What is the practical significance of blood-sugar curves in connection with mental disorders? It is possible that they may be just one expression of a general causative disordered metabolism; the association of fat and carbohydrate metabolism has been mentioned, and it is probable that with appropriate investigations further important metabolic defects may be discovered. There is no definite association with prognosis in mental condition; progressively deteriorating cases may give normal or abnormal curves, but in certain types of acute psychoses with markedly abnormal blood-sugar curves there may be a return to the normal type of curve coincident with recovery. Also the blood-sugar curve may be taken as a guide to the efficiency of treatment, especially with regard to gland therapy, and the question of acid and alkali treatment by drugs or diet under the same guidance may be worthy of consideration. The feature of the blood-sugar curve in the normal is its constancy, and treatment that brings the abnormal curve nearer to normal limits may be associated with clinical improvement.

In conclusion, I would express my indebtedness to Dr. Golla for his unfailing interest, to Dr. Mapother and the medical officers of the Maudsley Hospital for access to their cases and for their helpful

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encouragement, and to the volunteers who provided me with normal control experiments from time to time.

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