STUDIES IN EPILEPSY.*

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Hippocrates was the first to regard epilepsy, not as a " sacred disease ", but as a disorder due to natural causes. He believed that a causal relationship existed between humidity of the brain and the epileptic crisis—a hypothesis that in recent years has assumed prominence following the work of Temple Fay (27) and McQuarrie (28). According to Fay an abnormal increase in intracranial pressure is brought about by the accumulation of fluid over the cortex, due to impairment of function of the Pacchionian bodies.

The majority of recent workers have, however, concerned themselves directly or indirectly with the rôle played by cerebral vascular disturbances. An extensive review of the literature is given by Lennox and Cobb (29), who suggest that the most probable explanation of the convulsion is cerebral arterial spasm, causing decreased capillary blood-flow. This would produce, firstly, deficiency in oxygen supply, with consequent alkalosis of the brain, and secondly, œdema resulting from the increased passage of fluid outwards through the capillary walls.

The present investigation is concerned with both clinical and biochemical aspects of the subject, and is accordingly divided into two parts. In Part I an assessment is made of the value of vaso-dilator substances in the treatment of epilepsy, while Part II comprises a study of the regulation of acid-base equilibrium of the blood by epileptics and its relation to seizures.

Part I.—The Rôle of Vascular Spasm.

Acetyl Choline and Pacyl in the Treatment of Epilepsy.

Since Hughlings Jackson (1), in 1870, pointed out the possibility of the epileptic seizure being determined by contraction of the cerebral arteries, the rôle of " vascular spasm " in this disorder has been a subject of clinical and experimental interest. Vascular spasm is a mechanism now accepted by many clinicians as explaining a number of cases of transitory aphasias, hemianopias and migraine. The sudden blanching of the extremities as a result of

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vaso-constriction is well illustrated in Raynaud's disease. The association of Raynaud's disease with cerebral vascular disturbances has been recorded by Norman (2) and by Carp (3). Russell (4) has noted the similarity between the stages of the epileptic convulsion and the symptoms accompanying heart-block in Stokes-Adams' disease.

Many observations of the exposed cortex during epileptic attacks have been made. Foerster (5) describes the sequence of events repeatedly seen by him on the operating table. Sudden pallor of the cortex and arrest of cerebral pulsation is immediately followed by extreme hyperæmia, venous engorgement, and bulging of the brain. Horsley (6), Leriche (7), Kennedy and Hartwell (8) have observed similar changes. Corroborative evidence is to be found in the observations of the fundus oculi during an attack. Jackson (9), as long ago as 1863, noted that the fundus was pale before a seizure, and that during the convulsion the veins became large and dark.

Experimental evidence has recently been brought forward to show that the cerebral vessels contract after stimulation of the cervical sympathetic and dilate in response to vagus stimulation (Schilf (10), Forbes and Wolff (11)). The effect of these observations has been to bring again to the foreground the hypothesis that fits are precipitated by cerebral vaso-constriction. But although it is now generally acknowledged that the cerebral arteries are under vasomotor control, a causal relationship between cerebral vaso-constriction and the epileptic attack is by no means accepted (Notkin *et al.* (12), Wilson (13)).

On the assumption that seizures are due to vaso-constriction of the cerebral arteries, various operations on the cervical sympathetic chain have been performed in epileptic patients (Alexander (14), Bojovitch (15), Tinel (16), Zavialoff (17), Lauwers (18)). The results of cervical sympathectomy have, on the whole, been disappointing. Favourable results in certain subjects are reported recently by Lauwers (19) following the removal of the carotid body.

Attempts to influence epileptic attacks by the administration of vaso-dilator substances have been made. Popea and Eustatziou (20) in 1927 recorded beneficial results following the inhalation of amyl nitrite at the onset of attacks. In 1929 Villaret and Justin-Besançon (21) demonstrated the therapeutic value of injections of acetyl choline in Raynaud's disease, arteritis and similar complaints. The beneficial effects of acetyl choline in Raynaud's disease appeared to lend support to the vaso-constriction theory of epilepsy. In 1931 Etienne (22) and his co-workers at Nancy investigated the action of this substance on a group of seven epileptics. In two cases a notable reduction in the incidence of fits was recorded. Later, de Gennes (23) reported that injections of acetyl choline arrested the seizures in two cases of status. Similar results were described by Pagniez, Plichet and Decourt (24). Bolsi (25), in 1932, reported a dramatic reduction in the number of seizures in five of his eight cases. In some of the group investigated, the beneficial effect persisted for several days after the injections of acetyl choline. On the other hand,

Dejean and Hughes (26) did not obtain any favourable results in four cases treated over a period of fourteen days.

Experimental.

The therapeutic effects of acetyl choline and of pacyl were investigated in fourteen cases of epilepsy. The cases selected were subject to frequent major convulsive attacks, which were unassociated with ascertainable organic disorder in the nervous system or elsewhere. The age at onset of the disorder and the age at the time of the investigation are recorded in the table. Either some degree of congenital mental defect or progressive mental deterioration was present in each member of the group. No change was made in the diet, usual medication or regimen of the subjects during the experiment. The type and frequency of all convulsions, auræ and equivalents were recorded for stated periods before, during and after treatment.

Acetyl choline bromide (B.D.H.) was administered by subcutaneous injection each morning for fourteen days. The initial dose given was 0·1 grm., followed by a daily dose of 0·15 grm. After seven days the dose was increased to 0·3 grm.

Pacyl is a derivative of choline and has the advantage of being administered orally. Its action as a parasympathetic stimulant is claimed to be more nearly constant than that of acetyl choline. Two pacyl tablets were given three times daily for fourteen days.

Table Showing Results of Treatment with Acetyl Choline Bromide and Pacyl.

Case No.	Age at onset.	Present age.	Number of seizures. During previous 14 days.	During pacyl treatment (14 days).	During acetyl choline treatment. (14 days).	During succeeding 14 days.	Remarks.
1	14	22	23	32	20	19	Unchanged.
2	7	31	34	29	30	41	,,
3	16	26	5	4	1	6	Improved.
4	7	23	5	4	3	4	Unchanged.
5	Inf.	30	7	8	3	1	Improved.
6	,,	39	4	4	4	3	Unchanged.
7	11	23	37	66	*—	—	Unimproved.
				During acetyl choline treatment (14 days).	During pacyl treatment (14 days).		
8	3	24	5	1	5	5	Improved.
9	3	29	3	1	2	4	,,
10	Inf.	33	2	0	2	1	,,
11	,,	21	5	4	5	5	Unchanged.
12	,,	18	2	12	12	4	Unimproved
13	,,	14	19	18	18	12	Unchanged.
14	12	20	9	7	9	8	,,

* Treatment stopped on account of increase in number and severity of seizures.

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Half the cases were first given a course of pacyl tablets, followed by a course of acetyl choline injections. In the other seven cases this procedure was reversed.

Discussion.

The influence of pacyl tablets and acetyl choline injections is shown in the table. No beneficial effect was observed during pacyl administration. During acetyl choline treatment it will be noted that in five cases a reduction in the number of seizures occurred. There was no association between the decrease in the number of convulsions and the increased dosage (0·3 grm.) given during the second week. In two cases diminution in the number of seizures was accompanied by an increase in psychic equivalents. No change in the type or severity of the seizures was observed in the other three cases, classified as improved. One of these (Case 8) became brighter and more energetic and this mental improvement was maintained for some weeks, although the number of fits again increased after treatment. There was no mental change noted in the other two cases that showed decrease in number of fits during the injections. Case 5, where a decrease in the number of seizures occurred during the fourteen days' period following acetyl choline administration, was confined to bed at this time. With regard to Case 7, a great increase in the number and severity of attacks coincided with the end of the pacyl treatment. An attempt to arrest the rapidly repeated seizures by two 0·4 grm. doses of acetyl choline failed and this form of treatment was in consequence stopped.

The results obtained in the seven cases classified as unchanged do not call for individual discussion.

Comment.

The question arises whether the beneficial effect occurring in the few cases of the group during acetyl choline therapy may not be dependent on some other factor than the action of this substance. It is well known that periodic fluctuations in the incidence of seizures occur in many epileptics. An investigation of the incidence of fits occurring in these cases during the previous three months, when the subjects were under the same conditions in all respects except for acetyl choline treatment, did not disclose any fourteen-day periods comparable with those which have been held to justify the use of the word "improved" in the table.

While, therefore, there was no dramatic reduction in the incidence of seizures, it would seem that a small proportion of the group were less susceptible to attacks when under the influence of acetyl choline.

The results obtained from the administration of the choline derivative, pacyl, were discouraging.

On the whole, it may be said that the results which followed the use of these

arterial antispasmodic substances do not lend support to the hypothesis that cerebral vaso-constriction is by itself the precipitating factor of the epileptic attack. It must, however, be admitted that the action of the drugs employed may not be the same in the case of the cerebral circulation as in the peripheral vessels of the body.

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Part II.—Acid-Base Equilibrium of Blood in Epilepsy.

In epilepsy much attention has been directed to metabolic changes which influence the incidence of seizures. It has been demonstrated that in certain cases seizures may be modified by measures which affect the acid-base balance of the organism, induced alkalinity favouring the number and severity of seizures and induced acidity having the reverse effect. In view of these observations, many attempts have been made to find a correlation between the physical condition of epileptics and a disturbance in the regulation of acid-base equilibrium of the blood.

It has been established by most authors that in the period between fits, variations in blood constituents are usually within physiological limits. Much confusion, however, prevails as to what takes place at the time of the actual seizure. Some authors, for example, claim that the fit is preceded by an increase in alkali reserve (alkalosis) and in pH (alkalæmia), others that the reverse (acidosis and acidæmia) takes place, while yet others have observed no appreciable change. The explanation of these diverse opinions lies in the fact that the normal variations in alkali reserve and pH of different individuals, and even of the same individuals at different periods, is of wide range, and it follows that sound conclusions can be drawn only from a large number of observations. The difficulty of obtaining a large number of

cases during and particularly preceding seizures is apparent. It appeared, therefore, that the most satisfactory way of approaching the problem was to attempt to obtain specimens of blood from individual patients immediately before, during and after a particular seizure, and to compare these with samples taken during the free intervals.

The clinical material selected for this study consisted of institutional cases of essential or idiopathic epilepsy with fits of frequent occurrence. The administration of drugs was discontinued, and careful observations made for twenty-four hours before specimens were taken. Notes were made during this period of all possible modifying factors, such as diet and previous medication, the mental and motor states of each patient, and the time and character of any sensations, auræ or fits. Samples of venous blood were taken from several patients at frequent intervals for a short time in the expectation that one of them might have a seizure shortly after a venepuncture. If this occurred, further punctures were made during and after the convulsive crisis. This procedure was successful on very few occasions, since the probability of a seizure taking place during the period of observation was slight. On the other hand, a number of specimens was obtained, representative of various inter-seizure periods.

A series of normal controls was obtained, and this was supplemented by healthy, high-grade defectives employed as ward workers in the mental institutions. The advantage of including these patients was that control specimens were thereby obtained under conditions identical with those of the epileptics, and could be analysed at the same time.

All subjects at the time of blood-sampling were in the post-absorptive state, and had rested for at least one hour.

Experimental.

Venepunctures, usually of the median basilic vein, were made without stasis, the blood being collected under paraffin in an air-tight syringe, and run immediately into tubes containing paraffin and a small amount of Evans's 9 : 1 mixture of potassium oxalate and sodium fluoride, previously moistened with two drops of saline. The blood was stirred gently with a thin glass rod and the tubes were then stoppered and placed in an ice-box. The blood-samples were allowed to stand in a refrigerator until sufficient plasma had separated out to be removed, under paraffin, without centrifuging. In this way any loss of CO_2 was minimized.

Estimations of alkali reserve, pH and lactic acid were carried out on the plasma.

Alkali reserve was determined by the titrimetric method of Van Slyke.

pH measurements were made by the electrometric glass electrode method. The apparatus used was that designed by Kerridge (41).

Lactic acid was determined by the method of Friedemann, Cotonio and Shaffer (35), modified by Friedemann and Kendall (36). The percentage recovery of lactic acid was between 95 and 98.

The results obtained fall into two sections:

(1) General statistical results, consisting of averages of a number of isolated samples; these are shown in Tables I–III.

(2) Results from successive venepunctures performed on individual cases before, during and after a particular fit; these are represented graphically in Figs. 1–3.

Discussion.

(1) General Statistical Results.

Alkali Reserve.

Divergent opinions have been expressed with regard to the alkali reserve content of the blood in epilepsy and its variation in relation to seizures.

Bigwood (31), in presenting a large amount of experimental evidence, concluded that in the period between fits, the blood bicarbonate rested within normal limits. Katzenelbogen (40) reported that the "interval" alkali reserve was within the normal limits of 54–74 volumes of CO_2% in 31 patients, and Lennox and Allen (42) found the plasma bicarbonate within 55 and 70 volumes CO_2% in 88 out of 100 patients. Ballif and Reznic (30) state that the alkali reserve was normal in the free interval and immediately before seizures, but fell after seizures.

Gozzano (38), however, found that in one-third of his cases the "interval" alkali reserve was higher than normal. Dautrebande (33) also noted an increased alkali reserve, but stated that this had no relation to the occurrence of fits.

Torres Lopez (47), on the other hand, found that the "interval" alkali reserve was normal in the majority, but diminished in about 30% of his cases. Villacien and Urra (48) report a diminished alkali reserve in the period preceding the fit. Puca (45) also found a lowered alkali reserve in the pre-paroxysmal phase, with further lowering in the period following the attack.

Di Renzo (34) presented findings which differed from those of the above authors, and suggested that the alkali reserve rose from the normal value twenty-four hours before the fit, reached a maximum a few minutes before the crisis, fell rapidly to the normal value immediately before, and remained normal during and after the fit. The results tabulated, however, particularly for the period immediately preceding the fit, are clearly too few for detailed critical examination.

The results obtained for alkali reserve in the present investigation are

TABLE I.—*Alkali Reserves of Venous Blood-plasma (vols. CO_2 per 100 c.c.).*

Case No.	Interval period.		2-hour pre-fit period.		During fit.		0 ½ hour after fit.		½ 2 hours after fit.	
	Number of observations.	Averages of alkali reserves.	Number of observations.	Averages of alkali reserves.	Number of observations.	Averages of alkali reserves.	Number of observations.	Averages of alkali reserves.	Number of observations.	Averages of alkali reserves.
1*a*	3	68·5	..	..	2	55	..	..	..	..
1*b*	7	70·5	..	..	..	..	..	..	..	..
1*c*	4	72·5	..	..	1	55	2	49	1	70
2	4	72	..	..	..	..	..	..	..	..
3	1	74	..	..	1	64·5	..	..	..	..
4	7	63·5	3	64·5	..	..	..	..	..	..
5	10	65·5	..	..	..	..	..	..	..	..
6	2	70	..	..	..	..	..	..	..	..
7	4	72	..	..	..	..	..	..	2	72·5
8	7	70·5	5	71	2	61	2	69·5	2	70
9	2	70	..	..	1	49·5	..	..	..	..
10	5	70	3	69·5	1	68	4	69	3	70·5
11	3	71	..	..	1	60	1	62	1	62
12	2	70·5	6	70	1	65·5	2	65·5	..	..
13	1	63	..	..	..	..	1	57	..	..
14	3	61·5	1	59·5	..	..	1	57·5	3	59
15	2	73	..	..	..	..	..	..	1	59·5
16	3	65	..	..	1	61·5	..	..	2	64·5
Highest individual result	..	78	..	74	..	68	..	71	..	73·5
Lowest individual result	..	58·5	..	59·5	..	49·5	..	44	..	57
Average of all results	70	*68·7*	18	*68·8*	11	*59·7*	13	*63·3*	15	*66·3*
Controls :										
Highest	..	73								
Lowest	..	57								
Average	12	*64·4*								

recorded in Table I. These show, firstly, that the alkali reserves of epileptics in the interval period fall, with very few exceptions, within normal limits. Secondly, the average for epileptics of 68·7 volumes %, compared with 64·4 volumes % for normals, indicates an increase in epilepsy. This, however, is regarded as merely suggestive, in view both of the wide variation in individual alkali reserves, and also of the fact that these patients have been subjected to courses of luminal and other drugs which might conceivably affect their alkali reserve content. Thirdly, there is no appreciable difference between the alkali reserves of epileptics in the interval period and those in the two-hour period preceding the fit. It should be pointed out that in the results tabulated for the latter period, no case has been included in which previous fits had occurred on the same day.

The period of the few minutes preceding the fit is of great importance, but the results for this phase are too few to warrant special treatment. It is clear, however, that there is a fall in alkali reserve during a fit, and by correlating clinical findings with the results, it was manifest that the degree of this fall was related to the severity of the convulsion. In cases of severe major fits the decrease in alkali reserve was continued for some minutes after the crisis, but even in these instances recovery to normal was usually completed within two hours.

Hydrogen Ion Concentration.

In contrast with the varied opinions concerning the levels of alkali reserve during epilepsy, there is comparative unanimity amongst authors with regard to the hydrogen-ion concentration of the blood-plasma. It should be noted that previous investigators have employed colorimetric methods for the determination of pH, and that these give higher results than those obtained by the electrometric glass electrode technique.

Jarløv (39) found that the blood of epileptics showed a tendency to increased alkalinity before the convulsive crisis, and that this was replaced by a decrease following the attack. The attack was regarded as being a defence reaction of the organism against alkaline intoxication. Geyelin (37) concluded that although there was no definite pH curve characteristic of epilepsy, these patients showed a wider daily range than did normals. Osnato and co-workers (43) found that the pH of the plasma in 29 cases was within the normal range, given as 7·33–7·44. Bigwood (31) reported an increased blood alkalinity preceding seizures and applied the equation of Rona and Takahashi (46), $Ca^{++} = K \frac{[H^+]}{[HCO_3^-]}$ to his results, concluding that the effect of increased pH (in the absence of a corresponding decrease in HCO_3 ions) was a reduction in Ca ions, which in turn precipitated the fit. Dautrebande (33) suggested that the high pH values obtained were due to the presence in the blood of

epileptics of an alkaline substance which combines with difficulty with CO_2 *in vivo*.

TABLE II.—*pH of Venous Blood-plasma.*

	Controls.	Epileptics. More than 2 hours before or after fit.	Within 2 hours before fit.	During fit.	0–½ hour after fit.	½–2 hours after fit.
Number of observations :	8	20	8	7	11	9
Highest	7·36	7·39	7·42	7·37	7·38	7·40
Lowest	7·30	7·30	7·32	7·15	7·28	7·31
Average	7·32	7·35	7·355	7·29	7·34	7·36

TABLE III.—*Lactic Acid of Venous Blood-plasma* (*mg./*100 *c.c.*).

	Controls.	Epileptics (during interval period).
Number of observations	8	8
Highest	18	18
Lowest	10	10
Average	13·5	13·0

The results recorded in Table II indicate a larger variation between the pH values of epileptics than exists in the normal The average pH in the two-hour period preceding the fit shows no significant rise from that in the interval period. On the average, however, epileptic plasma tends to be slightly more alkaline than normal, although, as in the case of alkali reserves, this is quite insignificant when applied to individual cases. During the fit there is a fall in pH, the extent of this being dependent on the severity of the seizure, and also on the time after the commencement of the fit that the venepuncture is made. In all cases the pH returns to normal limits in a short space of time.

Lactic Acid.

Very few determinations of blood lactic acid in epilepsy have been made by previous observers. Osnato and co-workers (43) found lactic acid values above normal for epileptics, and stated that this increase bears no relation to the time elapsing since the previous seizure and, therefore, is not due to the muscular exertion during convulsions. The figures recorded, however, are unreasonably high in a number of cases, and it is very unlikely that they would be obtained with the more refined experimental technique now available for determining lactic acid. Moreover, no experimental results for normal blood

lactic acid are given. Ballif and Reznic (30) argue, without presenting experimental evidence, that the fall in alkali reserve immediately after a fit is due to the production of lactic acid resulting from muscular contractions during the seizure.

The results recorded in Table III indicate that in the interval period between fits the lactic acid content of the blood-plasma of epileptics is normal. This contradicts the findings of Osnato.

(2) Individual Cases.

Case 1. (Fig. 1.)

During the morning of the day of investigation the patient had a series of attacks, consisting of major fits at 7 a.m. and 9.30 a.m., and minor fits at 10.30 a.m. and 11.10 a.m. She was still stuporose, but of a good colour and breathing quietly when the first blood sample was taken at 11.50 a.m. At 11.55 a.m. the patient became rigid and cyanosed, and developed generalized clonic contractions, lasting two minutes, before relaxing into a stuporose state. At 12 noon venepuncture was about to be made when the patient had another major fit. A puncture was performed during the seizure, and at 12.10 p.m. a third blood-sample was taken, the subject at this time being restless and over-active. She was still somewhat stuporose half an hour later, full recovery taking place in about two hours. No further attacks took place for six days.

Case 12. (Fig. 2.)

This patient had a moderate major fit at 9.15 a.m. on the day of investigation. A blood sample was taken at 11.45 a.m. At 12 noon the patient was pale and said that he was about to have a seizure. A venepuncture was performed, the patient being quiet and co-operative. At 12.15 p.m. he had a short aura, a sensation of coldness in the right leg and " buzzing " in the head. His eyes rotated upwards, the head extended and he fell, with generalized muscular twitchings lasting about 20 seconds. A blood sample was taken. The patient recovered quickly and spoke at once. Further venepunctures were made at 12.20 p.m. and 12.45 p.m.

Case 17. (Fig. 3.)

The seizure observed was the only one occurring on the day of investigation. A blood sample was taken at 12.40 p.m. At 12.52 p.m. the patient had a severe major fit with muscular contractions, lasting over two minutes. A venepuncture was made during the fit. Recovery of consciousness took several minutes, the patient then becoming confused and over-active. Further blood samples were taken at 1.2 p.m. and 1.12 p.m., by which time the patient was quiet.

It is clear from a consideration of the graph of Figs. 1–3 that the fall in alkali reserve follows closely the increase in lactic acid, and that subsequent recovery of alkali reserve accompanies the removal of lactic acid. The relation between these is further demonstrated by comparison with Fig. 4, in which " exercise curves " given by normal individuals exhibit the same features. It is evident that the change in alkali reserve caused by the epileptic crisis is

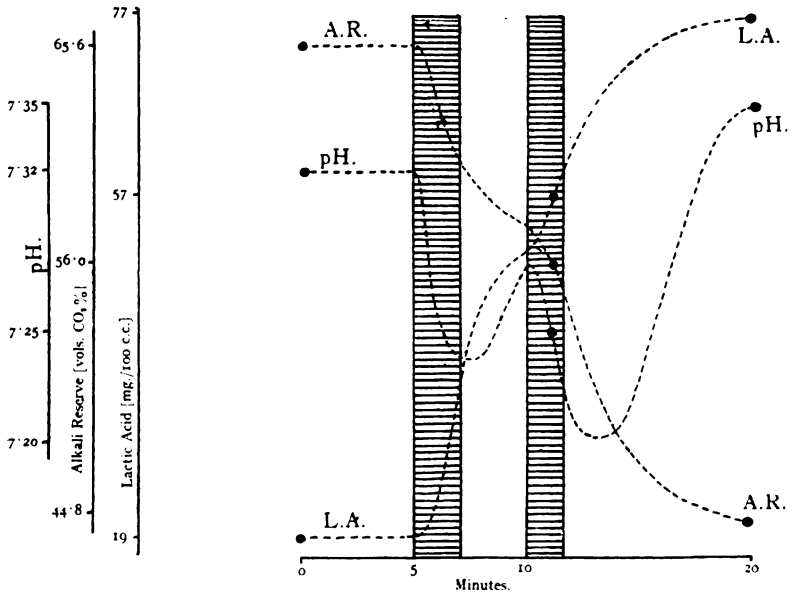

FIG. 1.—CASE 1.—Two severe major fits within seven minutes.

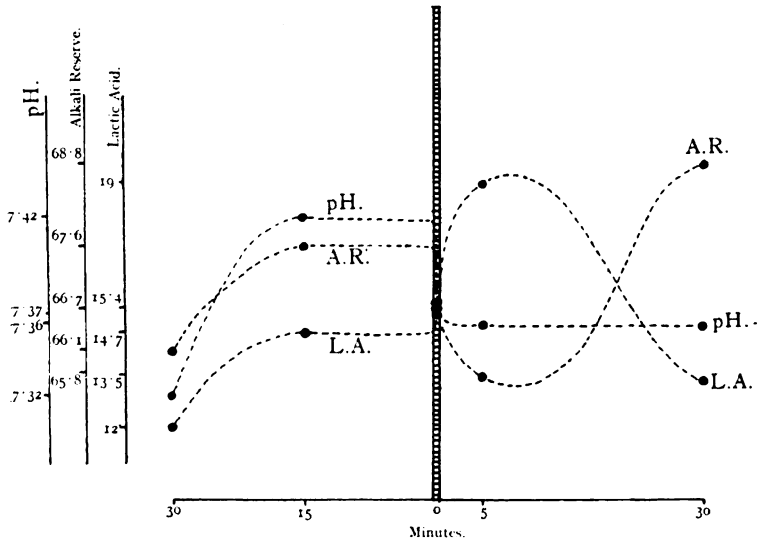

FIG. 2.—CASE 12.—Moderate major fit (20 seconds).

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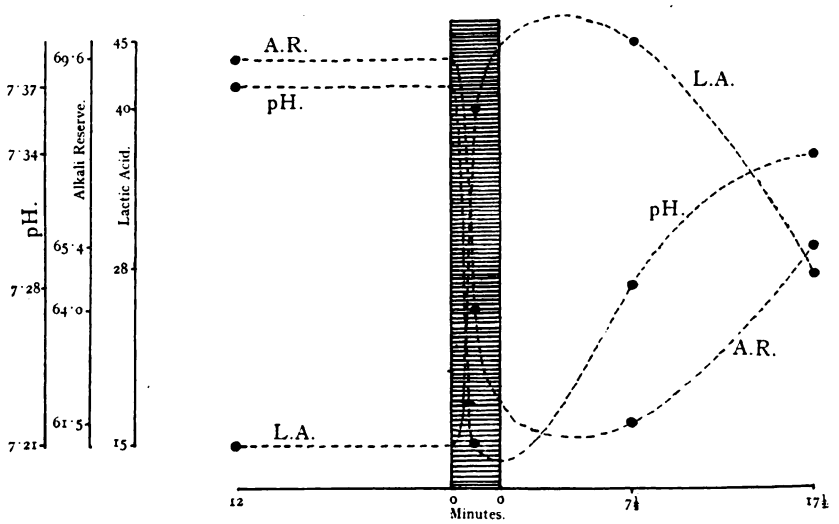

FIG. 3.—CASE 17.—Severe major fit.

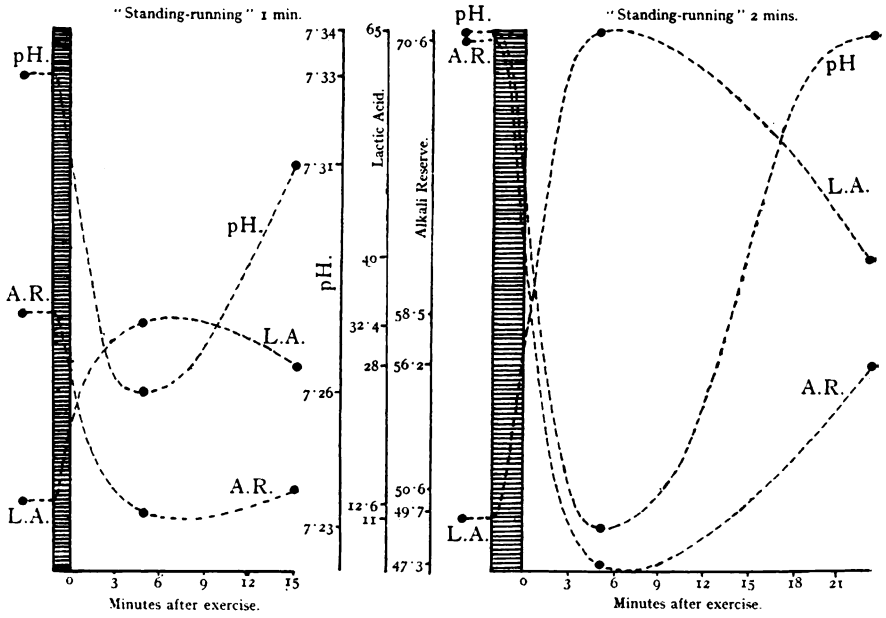

FIG. 4.—Normal exercise curves.

accounted for very largely by changes in the concentration of lactic acid in the blood.

The amount of lactic acid accumulating in the blood as a result of muscular contractions is related to the efficiency of the recovery process, in which energy derived from the oxidation of a part of the acid is used in the re-synthesis to glycogen of the remainder. The first stage of the epileptic fit produces anoxæmia, and this impairs the efficiency of the bodily mechanisms (chiefly liver and muscles) for dealing with the removal of lactic acid. Moreover, many of the muscles involved in the production of lactic acid during the convulsion are not accustomed to dealing *in situ* with large quantities of this substance, and it has been well established by Bock and co-workers (32) and by Owles (44) that training is of considerable importance in preventing the leakage of lactic acid into the blood after muscular contractions. There is, therefore, good reason to expect the presence of large quantities of lactic acid in the blood as a result of severe seizures, and comparison of Figs. 1 and 4 shows that the blood lactic acid was higher after two consecutive fits than after the very severe exercise of a " standing run " for two minutes to the point of exhaustion.

The depression of pH during the fit is due firstly to the retention of CO_2 during the tonic stage, and secondly to accumulation of lactic acid during the clonic stage. These have additive effects in increasing the amount of free CO_2 in the blood, and in the case of a severe fit may lead to over-stimulation of the respiratory centre. This is shown in Fig. 1 by an increase in pH a few minutes after the fit to a level higher than the pre-paroxysmal one, in spite of the continued accumulation of lactic acid in the blood. In the case of normal individuals after exercise, on the other hand, recovery to the normal pH appears to be a more gradual process.

It appears almost certain from the above results that changes in the blood constituents described in this dissertation are the result of, and in no way the cause of, epileptic seizures.

Summary of Part II.

(1) The acid-base equilibrium of the blood in epilepsy has been studied, measurements being made of pH, alkali reserve and lactic acid.

(2) The results suggest that in the interval period between fits—

(*a*) Variations in alkali reserve and lactic acid are usually within normal limits, but those of pH extend to a range slightly above normal.

(*b*) The average lactic acid concentration is normal. The average alkali reserve and pH values are slightly above normal.

(3) The averages of results obtained for alkali reserve and pH during the two-hour period preceding the fit show no significant difference from those of the interval period.

(4) Results obtained from blood-samples of individual patients before, during and after a particular seizure are illustrated by graphs, and lead to the following conclusions :

(*a*) There is a fall in alkali reserve during and for varying periods after the fit, this fall being accounted for by the accumulation of lactic acid in the blood. Decrease in lactic acid during recovery is accompanied by increase in alkali reserve.

(*b*) The blood pH falls during the fit, due firstly to apnœa during the tonic stage, and secondly to production of lactic acid during the clonic stage. Recovery to the normal pH is more rapid than in the case with normal individuals after exercise.

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Appendix.

Notes on Individual Cases Investigated in Part II.

Case 1 : *Idiopathic epilepsy.*—W. F—, girl, æt. 22, admitted January 18, 1930.

Family history.—Mother alcoholic. Patient an only child. There is no known history of epilepsy, mental defect or insanity.

Previous history.—Birth, infancy and childhood apparently normal. At the age of 14 patient began to have epileptic fits, which gradually increased in frequency. Menstruation began normally at the age of 14, but stopped following a fright at 17. Increase in the number and severity of the attacks, with periodic maniacal outbursts, led to certification two years later. Attacks, mostly major, now average 30 per month. Gradual development of typical epileptic habitus : dull, stupid and obstinate.

Physical.—No abnormality of skull. Optic fundi normal. No cranial nerve lesion ; no muscular weakness or spasticity ; deep and superficial reflexes normal ; no sensory impairment. No evidence of disease of heart, lungs or abdominal organs. Wassermann reaction of blood negative. Urine contains no abnormal substances. Blood-pressure 98/70.

Case 12 : *Idiopathic epilepsy.*—R. W—, porter, æt. 23, admitted August 22, 1930.

Previous history.—Labour was normal and no instruments were used. He attended school till the age of 12, when he began to suffer from fits, with generalized muscular spasms and loss of consciousness, followed by a short period of stupor. There is no known history of head injury and no family history of epilepsy or insanity.

A year before admission a seizure occurred when the patient was in a swimming-bath, and this was followed by pneumonia. He was taken to a general hospital, where he had 100 fits in a few days, followed by profound confusion and restlessness. Fits now average 40 per month.

Physical.—A short, well-developed man, with slight exophthalmos. Repeated examination of the nervous system has revealed no evidence of any organic disorder. No evidence of disease has been found in the lungs, heart or abdomen. Wassermann reaction of blood negative. Urine contains no abnormal constituents. There is no skull abnormality. Blood pressure 110/75.

CASE 17: *Idiopathic epilepsy*.—S. B—, æt. 28, admitted October 11, 1919.

Previous history.—"Convulsions" were noticed at the age of 18 months, the patient's mother attributing these to a fall on the head occurring at this time. At the age of 10 the patient was sent to an epileptic colony. There was a gradual increase in the frequency of attacks, of the typical *grand mal* type. He became very dull and retarded, and was removed to a mental hospital. Fits now average 15 per month.

Physical.—There is no evidence of organic disorder in the nervous system or elsewhere. Wassermann reaction of blood negative.