BACTERIAL CHANGE IN MENTAL DISORDER: THE BACTERIAL DIGESTION OF TYROSINE.

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In a previous paper (*Journ. Ment. Sci.*, April, 1928, p. 269) the writer has pointed out that a culture tube of tyrosine bouillon, if inoculated from the fæces of a healthy person, incubated for forty-eight hours and distilled, will be found to contain not more than 0·008% of phenol, or at most 0·015%. If, on the other hand, similar cultures are made from mental patients they will contain 0·02 to 0·03% of phenol in one half of the persons examined. In all these cases the phenol is formed by the action of bacteria on the tyrosine in an alkaline medium. The most important phenol-producing bacterium in the insane is *B. Morgani*, which can be demonstrated in 25% of acute cases, while *B. phenologenes*, Berthelot, is found in a smaller number. The paper referred to dealt with the toxic effects of *B. Morgani* and the results of vaccination with this organism. In the present paper another aspect of the matter will be considered, namely, the production of tyramine from tyrosine by intestinal bacteria, and whether poisoning by this substance may be a cause of mental disturbance.

Bacteria which form phenol from tyrosine in an alkaline medium form tyramine from it in an acid medium containing a fermentable carbohydrate such as glucose or glycerine. On this subject Hanke and Koessler (1924, p. 867) write: (1) All colon bacilli which decarboxylate tyrosine to tyramine in an acid medium with carbohydrate, form phenol in an alkaline medium. (2) A colon which splits histidine into histamine in an acid medium does not form phenol in an alkaline medium. (3) Of the large group of neutral colons splitting neither histidine nor tyrosine, none have been found to give phenol.

We may therefore assume that bacteria which give rise to phenol in alkaline culture produce tyramine in the acid contents of the large intestine and perhaps also in the small intestine, where tyrosine, glucose and glycerine are to be found together. In fact phenol in the test-tube indicates tyramine in the bowel.

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Physiological and Pathological Action of Tyramine.

Barger (1914) states that tyramine or p-hydroxyphenylethylamine resembles adrenaline in its action, but with only one-twentieth of the potency of the latter; doses of 1–2 mgrm. injected intravenously cause a sudden and pronounced rise of blood-pressure, somewhat less transitory than that caused by adrenaline; the output of the heart is increased; the non-pregnant uterus relaxes, the pregnant uterus contracts; the salivary glands are stimulated. Its action is sympathomimetic, 100 mgrm. hypodermically to a cat gave all the symptoms of intense stimulation of the sympathetic nerves, but no after-effects or glycosuria.

The base acts so much like ergot that some writers have described it as the chief pressor constituent of certain extracts of ergot (Barger and Dale, 1909).

W. H. Harvey (1911) found that prolonged dosing with tyramine, either by mouth or vein, caused vascular sclerosis and secondary chronic nephritis in rabbits.

Experiments on animals are, however, of little value in determining whether the amine has any action on man, and more especially on his highest nerve centres and endocrine organs. In our present studies we are dealing not with normal man, but with those possessing an unstable nervous system. But helpful experiments have been provided on a fairly large scale by various epidemics of ergot poisoning in man, the latest of which is especially valuable since it affected a Jewish community that may be assumed to include a fair number of potential neuropaths. This epidemic is reported by Robertson and Ashby (1928), the symptoms being as follows: Coldness and numbness of the extremities, loss of touch and pain sensation in the fingers, formication and itching, nervousness, depression and headache, abdominal pain, staggering gait and ataxia, and rise of blood-pressure in some cases of long-standing to 174 mm.

The present paper, then, concerns itself with suspected tyramine poisoning, but it must be remembered that tyramine is only one of several ptomaines which may be formed by bacterial action in the intestine, and that if tyramine is not demonstrable in any one case it is still possible that some other amine, such as histamine, may be causing the symptoms. Therefore we must not expect a high phenol percentage in all cases, and even the same patient might suffer from poisoning by tyramine in one attack, with a high phenol percentage, and by histamine in the next, with low phenol. In the same way in recurrent coliform cystitis the infecting bacterium may be a lactose-fermenter in one attack and a

non-fermenter in the next. The common factor in each of the two attacks is an unstable nervous system in the one case and a bladder of low resistance in the other.

The previous literature on the amines contains many important papers which cannot be summarized briefly; they will, therefore, be referred to only in the bibliography at the end of this article. Suffice it to say that none is conclusive on the practical point at issue, *viz.*, whether disease is caused by the amines which are acknowledged to be present in the bowel. Two papers are, however, of special interest for our present discussion, *viz.*, Mellanby, 1911, which suggests that cyclic vomiting of children may be due to histamine, and Eustis, 1912, which attributes spasmodic asthma to the same base.

Section A.

The Phenol Percentage in Mental Patients compared with Sane Controls.

Sixty-five patients have been examined, in 33 of whom more than one examination has been made (162 observations in 33 cases), and in 32 only one examination. The series of sane controls consists of 28 male members of the staff of this hospital (Table I and Fig. 1). For each person one phenol reading only has been taken and that is the highest which he has given. The reason for this limitation will appear in the next section.

In Fig. 1 the base-line scale represents phenol percentage, the vertical gives the percentage of persons in the series at each degree of phenol. It will be seen that in the control series the curve begins at no phenol in 10·7% of the cases, rises abruptly to a

Table I.

Phenol, %.	Mental patients, acute.		Sane controls.	
	Number.	%.	Number.	%.
0·06	2	3	..	..
0·04	2	3	..	..
0·03	10	20	..	..
0·025	3			
0·02	11	24·6	2	7·14
0·015	5			
0·01	1			
0·0075	12	24·6	10	35·7
0·006	3			
0·005	7	21·54	9	46·42
0·002	7		4	
0·00	2	3	3	10·7
	65	99·74	28	99·96

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maximum at 0·002–0·005% phenol in 46·42% of the cases, drops steeply through 0·01 to 0·02 in only 7·14% of the cases. The mental series, on the other hand, shows a greatly flattened curve extending as far as 0·06% phenol, the number of persons at the four readings 0·005, 0·01, 0·02 and 0·03 being nearly equal. The actual numbers in the two series are given in Table I, and it will be seen that one half of the mental patients show a wide departure from the normal.

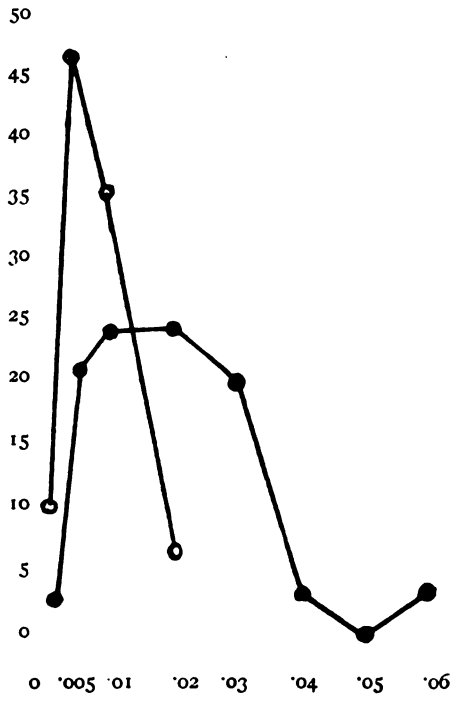

FIG. 1.—● Mental patients. ○ Controls.

SECTION B.

Table II deals with those mental patients of the series who gave any single phenol reading of 0·015% or over. The figures show the number of observations made on each patient, and these are divided so as to show whether high phenol readings occur in acute phases of illness and low readings in subacute as we would expect. It will be seen that the expectation is fulfilled since practically all the high readings occur in acute phases.

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TABLE II.

Case No.	Reading of acute phase.		Reading of subacute phase.	
	0·015% and over.	Below 0·015%.	0·015% and over.	Below 0·015%.
1	2	2	0	2
2	2	1	0	9
3	4	5	2	17
4	14	1	0	1
5	10	3	0	1
6	3	2	2	3
7	3	1	0	5
8	1	0	0	7
9	4	0	0	1
10	1	3	0	0
11	1	0	0	1
12	0	0	1	2
13	1	1	0	0
14	1	1	0	0
15	1	1	0	0
16	1	1	0	0
17	1	0	0	1
18	1	3	0	3
19	1	3	0	0
20	2	2	0	0
21	8	2	0	0
22	0	1	2	1
23	1	0	0	1
24	1	1	0	0
25	0	0	1	1
26	0	0	1	0
27	1	0	0	0
28	1	0	0	0
29	1	0	0	0
30	1	0	0	0
31	1	0	0	0
32	1	0	0	0
33	1	0	0	0
	71	34	9	56

SECTION C.

We now come to consider the individual cases. The first six have been recorded in my previous paper, and of these only the continuation of Cases 3 and 4 will be given here (see Table III).

In the cases given in Table IV no phenol-producing bacteria were isolated by plating on McConkey's medium. The phenol is probably formed by bacteria of the acidophilus-bulgaricus group.

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TABLE III.

Case No.	Date.	Phenol, %.	Phenol-producing bacteria isolated.	Clinical notes.
3	8.iii	0·0005	Paracolon	Recurrent mania in interval.
	16.iii	0·003	..	Morgan vaccine ½ and ¼ c.c. intravenously.
	29.iii	0·003	..	Mild mania 25.iii to 2.iv.
	16.iv	0·008	..	Interval.
	23.iv	0·001	..	Mania begins. (Purgative.)
	25.iv	0·0075	..	Mania.
	1.v	0·025	*B. Morgani*	,, Constipated.
	10.v	0·0001	..	Interval.
	12.v	0·01	..	,,
	14.v	0·01	..	,,
	16.v	0·0075	..	,,
	19.v	0·025	..	,, Constipated.
	20.v	0·01	..	,, After calomel.
	23.v	0·01	..	,, Constipated.
	25.v	0·0002	..	,,
	26.v	0·025	..	Prodromal stage. Not constipated.
	27.v	0·00	..	Mania early. After calomel.
	29.v	..	..	Profuse urticaria.
4	31.iii	0·03	..	Acutely suicidal from February to end of March, then into stupor.
	2.iv	0·06	*B. Morgani*	Enema on alternate days.
	8.iv	..	..	⅟₇ c.c. Morgan vaccine intravenously, reaction to 104° F.
	10.iv	0·02	..	..
	13.iv to 29.iv	0·03 to 0·01	*B. Morgani*	Stupor continuing.
	13.v	..	..	,, ended suddenly.
	16.v	0·0075	..	Almost normal mentally.
7	31.i	0·02	*B. Morgani*	Acute melancholia. Morgan vaccine ½ c.c. twice.
	24.ii	0·03	..	..
	10.iii	0·0075	..	..
	16.iv	0·005	..	Slow improvement.
	22.iv	0·0002	..	..
	25.iv	0·0075	..	..
	30.iv	0·01	..	..
	15·iv	0·004	*B. communior*	Marked improvement.
8	13.iii	0·04	*B. Morgani* *B. mutabile*	Acute dementia præcox.
	2.iv	0·005	..	..
	16.iv	0·004	..	Becoming subacute.
	22.iv to 14.v	0·0075 0·0001	..	Subacute.
9	17.ii	0·02	*B. Sonne* non-agglutinable by standard serum	Recurrent mania with asthma, acute.
	21.ii	0·02	..	Acute.
	25.ii	0·02	..	,,
	29.ii	0·02	..	,,
	24.vi	0·001	..	Interval, no mania or asthma.

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TABLE III—*continued.*

Case No.	Date.	Phenol, %.	Phenol-producing bacteria isolated.	Clinical notes.
10	26.iii	0·025	*B. Morgani*	Acute melancholia.
	4.iv	0·002	..	Less acute.
	to 15.v	0·001		
11	23.ii	0·002	..	Insanity with epilepsy, chronic.
	25.v	0·015	*B. communis and communior*	Series of fits with confusion.
12	19.i	0·0075	..	Idiocy with epilepsy, bromidrosis.
	1.ii	0·025	*B. Morgani*	1 fit in February, 1 in April.
	14.v	0·00	..	No fits in May.
13	9.i	0·002	..	Mania.
	13.iv	0·02	*B. Morgani*	Acute, readmitted.
14	25.iii	0·00	*B. mutabile*	Epilepsy. Very constipated.
	26.iii	0·015	..	After enemata.
15	8.xii	0·02	*B. Morgani*	Hysterical insanity, acute.
	10.i	0·004	..	Subacute.
16	19.iii	0·02	*B. communior*	Dementia præcox, acute.
	29.iii	0·01	..	..
17	2.iii	0·03	*B. acidi lactici*	Agitated melancholia.
	16.iv	0·002	..	Feeble and bedridden.

TABLE IV.

Case No.	Date.	Phenol, %.	Clinical notes.
18	26.ix	..	Recurrent mania, just relapsed.
	2.xii	0·02	..
	17.xii	0·0075	Mania ends.
	30.xii	0·004	Interval.
	21.i	0·004	,,
	23.iii	0·00	Just relapsed.
	26.v	0·002	Interval.
19	31.xii	0·0075	Recurrent mania, relapsed on 30.xii.
	5.i	0·0075	..
	9.i	0·002	..
	10.i	0·0075	..
	23.iii	0·01	Just relapsed.
20	5.xii	0·03	Acute dementia præcox, with pallor, high unstable blood-pressure, dilated pupils.
	7.xii	0·004	..
	21.i	0·004	..
	24.ii	0·03	..

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TABLE IV—*continued.*

Case No.	Date.	Phenol, %.	Clinical notes.
21	7.xii	0·03	Insanity with epilepsy in mania.
	23.i	0·0075	In mania.
	23.ii	0·03	,,
	27.ii	0·02	,,
	5.iii	0·025	In mania.
	19.iii	0·008	After mania.
	27.iii	0·02	Before mania.
	17.vi	0·003	After mania.
22	21.ii	0·02	Dementia præcox with recurrent mania in interval.
	8.iii	0·025	,, ,, ,, ,, ,,
	17.iii	0·007	,, ,, ,, ,, ,,
	12.vi	0·004	In mania.
23	23.ii	0·015	Epilepsy, after fits.
	24.v	0·0075	Interval.
24	6.xii	0·02	Dementia præcox, chronic.
	23.i	0·0075	,,
25	28.xii	0·0075	Neurasthenia with delusions.
	25.v	0·0015	,,

Through the kindness of some friends in practice I have had the opportunity of examining two cases of pernicious anæmia, two of asthma and one of migraine. Pernicious anæmia was chosen because of the resemblance in symptoms between subacute combined degeneration and ergot poisoning.

Pernicious anæmia, two cases, phenol 0·01, *B. coli communis phenologenes* in one.
Asthma, Case 1, during interval, phenol 0·002, during attack 0·0075.
,, Case 2. after attack, phenol 0·015.
Migraine, 1.v, during attack, phenol 0·02, *B. lactis acrogenes phenologenes.*
,, 24.v, during interval, phenol 0·001.

It could be said that the increase of phenol percentage is due merely to the constipation which accompanies the mental illness or to the purgation used to overcome this state. One of the normal controls was habitually constipated and constantly used purgatives, but cultures in his case gave phenol readings *nil* and 0·0015. Highly constipated stools may give very low, medium or high phenol, and stools passed after drastic purgation may do the same, while stools of normal appearance passed after several days of regularity may give high phenol.

It is obvious that one crucial question still remains to be answered, namely: Does the rise of phenol percentage precede or at least coincide with the onset of the illness or does it occur in the fully

developed illness? In the former case it may be causal, in the latter it is merely symptomatic.

Another line of work must also be completed, *viz.*, the examination of cultures in various amino-acids for the corresponding amines, and the quantitative estimation of the latter by simple phsyiological methods if they are found.

Technique.—The tyrosine medium used consists of bacteriological bouillon made with Lemco, but in which peptone is replaced by tyrosine 0·1%. The highest yield of phenol is obtained when the hydrogen ion concentration is from 7·5 to 7·8.

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