ALIMENTARY TOXAEMIA IN EPILEPSY.

A THESIS

for

THE DIPLOMA OF DOCTOR OF MEDICINE

of

THE UNIVERSITY OF GLASGOW

by

Dr F. E. Stokes.

—o—

THE CORPORATION MENTAL HOSPITAL,
PORTSMOUTH.

May 30th 1914

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Alimentary Toxaemia in Epilepsy.

The causation of Epilepsy is a subject concerning which there is much controversy, and includes a variety of factors embracing heredity - pathological anatomy and chemical pathology. In the following thesis I shall limit my observations to one factor - namely alimentary toxaemia and will endeavour to answer the question whether or not intestinal auto-intoxication has any relationship to the onset of the Epileptic attack or series of attacks - whether or not it has any relationship to the various phases met with in Epilepsy; and with regard to this investigation the subjects on which the following observations have been made were all epileptics who were certified insane.

Autointoxication may be defined as a toxaemia caused by substances which are formed through the influence of vital processes of the organism. There is a qualitative or quantitative alteration in the normal and bacterial digestion.(1) Only the toxaemia resulting from the breaking up of the protein molecule will be here considered.

The structure of the Protein molecule will first be inquired

(1) Combe "Alimentary Toxaemia".

into and later the question of its metabolism considered.

Classification of Proteins:- (1)

Proteins may be divided into the following classes:-

1. Protamines.
2. Histones.
3. Albumins.
4. Globulins
5. Scleroproteins.
6. Phosphoproteins.
7. Conjugated proteins.
8. The derivatives of proteins produced by hydrolysis.
    (a) Metaproteins.
    (b) Proteoses.
    (c) Peptones.
    (d) Polypeptides.
    (e) aminoacids

Structure of the Protein Molecule. (1).

The protein molecule is one of great complexity and is composed of a variety of aminoacids - which fall into certain groupings :-

1. Fatty Series

    (a) Monamino acids (monobasic)

        Ex. Glycerine or Glycocoll (aminoacetic acid)

        " Alanine (a. amino propionic acid)

(1) Handbook of Physiology. W.D. Halliburton
Principles of Physiology - Starling.

Serine (amino oxypropionic acid)

Leucine (amino isobutyl acetic acid)

(b) Monoamino Derivatives of Dibasic Acids.

Ex. Aspartic Acid (a. amino succinic acid)

Glutamic Acid (a. amino glutaric acid)

(c) Diamino Acids.

Lysine (a. e. diamino - caproic acid)

Arginine

Ornithini (diamino valerianic acid)

2. Amino Acids containing an aromatic nucleus.

Tyrosine (para-oxylphenyl a. alanine)

Tryptophone (indol-amino propionic acids)

Phenylalanine (phenyl a. amino propionic acid)

3. Amino Acids of Heterocyclic Compounds.

Proline = (a. pyrrolidin carboxylic acid)

Oxyproline

Histidine (a. amino propionic acid or iminazol alanine)

4. Sulphur containing amino-acids.

Ex. Cystine

5. Other constituents of the Protein Molecule.

Glucosamine

The Metabolism of the Protein Molecule. (1).

(The protein molecule is dissociated in the body and broken down ultimately into Carbon Dioxide, Water, Sulphates, Urea and Creatinine)

1. The action of acids on albumin gives rise to the following products

   1. Diamino Acids or hexone bases
   2. Ammonia.
   3. Mon-amino Acids.
   4. Aromatic Series (Phenyl Amino propionic acid or phenylalanine
      Tyrosin . and indol aminopropionic acid or tryptopham
   5. Fatty series Leucine - Glycoll - Alanine

2. The action of alkalies on albumin gives rise to the following products

   1. 2. 3. 4. 5. as above.
   6. Fatty acids acetic-valerianic - butysic.
   7. Aromatic Bodies.
      (a) Aromatic oxyacids (paraoxyphenyl acetic acid)
      (b) The phenols (paraoxyphenyl propionic acid)
      (c) Indoxyls skatoxyls.

3, Action of Gastric Digestion on Protein, gives rise to

   1. non crystalline bodies albumose peptones.
   2. Ammonia.
   3. Diamino Acids (Lysin-arginine-histidin)
   4. Mon-amino Acids
   5. Aromatic Series (Tyrosin, Tryptophan, phenylalanine)

(1). Intestinal Intoxication (Combe)

6. Fatty Series (Leucin, Glycoll, Alanin, Glutamic acid)

5. Action of Bacteria on Proteins produces

1. Non crystalline bodies - albumoses - peptones.

2. Ammonia.

3. Diamino acids.

4. Monamino acids,

5. Aromatic Series,

6. Fatty Series

7. Fatty bodies (a) Butyric caproic, valerianic acids

(b) ptomaines.

8. Bodies of the Aromatic Series.

a. oxyacid group para-oxyphenyl acetic acid

b. Phenol group phenol and paracresol.

c. Group of the indoxyls - indol and skatol.

9. Gases - Methane - Hydrogen - Carbon Dioxide

Sulphuretted Hydrogen - Methyl mercaptan

Products of the disintegration of the Protein Molecule.

Peptones :- are produced by hydrolysis by acids and alkalies and by bacterial putrefaction.

Ammonia :- is produced by the cells of the mucous membrane lining the stomach and intestinal walls . also during proteolytic

early metabolism and bacterial intestinal putrefaction.

Monamino Acids a. Monobasic - (Glycoll, Alanine, Serine, amido valerianic acid, Leucine)

b. Dibasic Aspartic Acid . Glutamic Acid.

(Leucine an early product of decomposition of protein, It is later decomposed into volatile acids by bacteria.)

Aromatic Series.

Tyrosin is decomposed by alkalies and proteolytic bacteria into phenols and cresols.

Tryptophan is formed parallely with tyrosin by the action of acids, alkalies and bacteria in proteins.

Phenylalanine is got from bacterial putrefaction of vegetable proteid, also from decomposition of casein by acids (Fischer)

Diamino Acids (Hexone bases)

LYSIN
Arginin } products of decomposition of albuminoid bodies by ferments (trypsin - erepsin)

The Pyrrol Group - Pyrrolidin - Carboxylic acid.

The Pyrimidine Group - Histidine -

The Carbohydrate Group - Glucosamine

Aromatic Substances.

Aromatic bodies (oxyacids, phenol, skatol, indol) are produced from the putrefaction of Nitrogenous foods in the intestine or from the secretions of the intestine. They may also be formed from suppurative lesions in the body and are increased in the urine when the patient is given phenol creosote &c.

Excretion of Aromatic bodies.

A small portion is excreted in the stools (skatol). Most enter the Portal circulation and are taken to the liver where oxidation and combination occur. Oxyacids are eliminated as such in the emunctories. Other aromatic bodies (phenols) combine with Sulphuric acid or Glycuronic Acid - others (indol, skatol) undergo oxidation first before combination.

Character of aromatic bodies.

1. Aromatic oxyacids.
2. Phenols.
3. Indoxyls.

1. Aromatic Oxyacids.

The digestion and putrefaction of proteids give rise to tyrosin. This

substance is acted on by bacteria and leads to the formation of aromatic

oxyacids (a) Paraoxy-phenyl acetic acid)

(b) Paraoxy-phenyl propionic acid.

(a) Is split into Para cresol and $C O_2$

(b) Is split into Para cresol and Phenol.

Their percentage increases with the intensity of intestinal putrefaction

Para oxy benzoic acid splits into Phenol and $C O_2$.

Homogentesinic Acid is produced from abnormal putrefaction of Tyrosin in the upper intestine. Only the first two of these substances are found free or as Salts in the urine, and only a small portion combines with $H_2 S O_4$ to form sulpho ethers.

Aromatic Acids.:

1. Phenyl acetic acid
2. Phenyl propionic acid
3. Hippuric [illegible] acid.

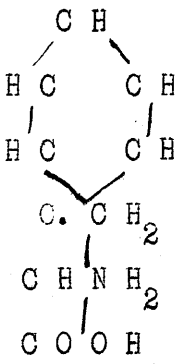
} Products of protein putrefaction.

1. Phenylacetic acid.

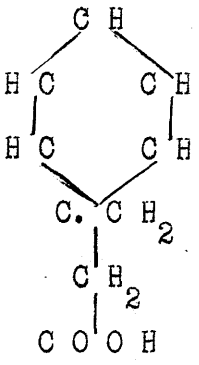
A secondary product of protein putrefaction which combines with Glycocoll to form phenaceturic acid.

2. Phenyl propionic acid, is produced from phenyl amino propionic acid (vegetable proteins) which is decomposed to phenyl propionic acid and this latter oxidized to Benzoic Acid and eliminated in combination with Glycocoll and Hippuric Acid. Hippuric acid augments with the intensity of intestinal putrefaction, but is not an index of it, as many vegetable substances give rise to Benzoic Acid.

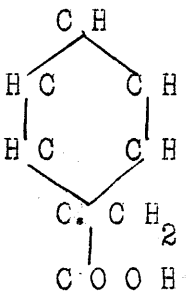
Phenylalanine



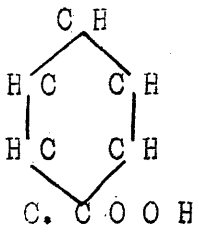
Phenyl propionic acid

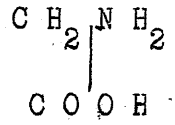


Phenyl acetic acid

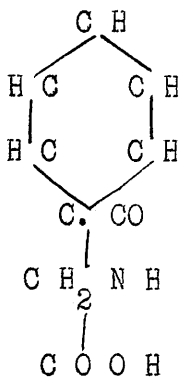


Benzoic Acid + GLYcocoll





Hippuric acid and water



Phenols:

are derived from tyrosin with the intermediary acids

(a) para oxy phenyl acetic acid

(b) para oxy phenyl propionic acid

Baumann(1) showed that putrefaction of tyrosin in proteins or intestinal juices produces a. and b. and these are changed to para cresol and phenol respectively.

Brieger(2) showed that para cresol was most frequently formed and phenol only in small amounts. No marked parallelism was noticed between the formation of phenols and indoxyl. In intestinal putrefaction phenol appears long after indol so at times much phenol is found and little indol and vice versa though as a rule the increase or diminution of

(1) Zeits. f. phys. Ch. IV (1880).
(2) " " " " (240).

these bodies run a parallel course.

Putrefaction of tyrosin in only got in the large intestine. In stasis of the small intestine only small amounts of phenols are got - the tyrosin not having entered the colon or only in small amounts, per contra in stasis of the large intestine phenols increase. Phenol may also be produced by the action of proteolytic bacteria on organic albumin - apart from intestinal elaborations.

Excretion of Phenols.

Phenols combine in the liver with sulphur formed from dissociation of albumen - to form sulpho ether acids (phenol sulphuric acid and cresol-sulphuric acid). If in excess they combine with Glycuronic acid. These are eliminated in the urine as Alkaline Salts. A portion is eliminated in the stools and Salkowskit maintains that a portion is oxidized in the organism.

3. Indoxyls.

Jaffé(1) showed that Indican was got from intestinal indol:-subcutaneous injections of indol were followed in a few hours by indicanuria.

Hufner and Kuhne showed that Indol was a product of bacterial putrefaction of proteins and Baumann and Brieger(2) showed that this putrefaction occurred in the intestinal canal.

(1) Centralbl. f. med. Wiss 1872 p.s.) (2). Zeits. f. phys Chem. p 254).

Hopkins and Cole showed that indol and skatol were produced from tryptophan. Ernst showed that part of indol is due to putrefaction of bile - intestinal and pancreatic secretions. Its amount is proportional to the amount of protein ingested - being increased with a meat diet and lessened with a vegetable diet, and if meat is taken in excess of one's digestive power and the assimilation of amino acids diminished and stagnation of the small gut occurs - then putrefaction increases and indol is formed in larger quantities in the intestine. Hirschler[1] showed that by adding carbohydrates to a meat diet, indol and skatol were diminished.

Site of production of indol in Intestine.

Jaffé[2] showed that ligature of the small intestine in animals produced an increase of indol, but that ligation of the large intestine had no influence on the production of indicanuria.

Ellinger and Prutz[3] came to the following conclusions, - that stasis in the lower portion of the small intestine increases indicanuria and stasis of the large intestine has no influence on its production: that stasis of the duo denum and upper portion of the small intestine is not accompanied by indicanuria and that progressive indicanuria is diagnostic of oncoming intestinal occlusion.

(1). Zeit.f.phys.ch X p.306.
(2). arch. Virch. LXX.
(3). Zeits f. phys ch. XXXVIII p. 199.

Ellinger and Geutsin (1) demonstrated that tryptophan fed or injected subcutaneously caused no increase in urinary indican, but injected into the caecum caused much indicanuria.

(1) Hofmeisters Beitr 1903 p. 171

As regards clinical observations, Nothnagel(4) showed that in chronic constipation - even if severe - indicanuria was not observed. Brieger and Ortweiler induced opium constipation and showed that indicanuria was not produced unless stasis of the small intestine occurred.

Indol may be formed outside of the intestinal canal - as Senator has shown that purulent collection s are accompanied by the formation of indol and skatol. It is very improbable that indol can be formed by the aseptic destruction of nitrogenous substances of the organism.

Elimination of Indol.

Indol is oxidized in the body into indoxyl - which combines in the liver with sulphuric acid to form Indoxyl sulphuric acid and this substance combines with Potassium and forms Indoxyl sulphate of Potash which appears in the urine.

The amount excreted, like phenols, depends on the composition of ingested food both as regards quantity and quality - the vigor of peristalsis - the power of absorption of the intestinal mucous membrane and the putrefactive intensity in the intestine. It diminishes with diminished appetite and is small in amount in affection of the large intestine and stomach and increases in stasis of the small intestine and with increased intestinal putrefaction.

(1). Handbuch XVII p672.

Skatol.

is derived from tryptophan and increases and diminishes parallely with indol.

Brenzcatechin.

Baumann[1] showed that this substance was formed in the intestine as an abnormal product of the oxidation of Phenol - so is produced from the aromatic protein nucleus. It combines in the liver with sulphuric acid and is eliminated thus in the urine.

Hydrochinon.

Is a product of the oxidation of phenol. It combines in the liver with sulphuric acid and is then excreted in the urine.

Alkapton.

was first found in the urine by Baedeker and identified with homogentisinic acid a product of the putrefaction of tyrosin and phenylalanin by Wolkow and Baumann.

8. The Putrefaction of Tyrosin, Phenylalanine and Tryptophan.[2]

In the putrefaction of Tyrosin the tendency is to retain the aromatic ring and to build down the fatty acid following deaminisation, thereupon the aromatic derivative is usually conjugated. In Catabolism in the tissues, the aromatic ring is ruptured and the entire molecule burned, so

(1) Zeits. f. phys. Chem. p. 523.
(2). Dyerlin Metabolism - A.E. Taylor.
(1) Zeits. f. phys. Chem. p. 523.
(2). Dyerlin Metabolism - A.E. Taylor.

that practically all the aromatic bodies of the urine are derived from bacterial decomposition of aromatic amino acids in the intestines.

The various stages may be stated as follows:-

1. Tyrosin is first deaminated.
2. The resulting p-oxy-phenyl propionic acid is oxidized to p-oxy-phenyl-acetic acid.
3. There is a reduction to phenol or cresol.
4. Some of the phenol is oxidized to Hydrochinon - a portion to ortho-dioxybenzene. These are eliminated partly as

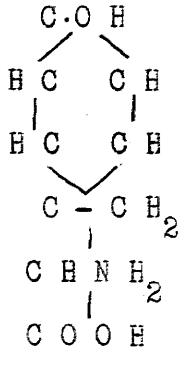
   (a) simple salts.

   (b) a large part as aromatic or ethereal sulphates (conjugated with $H_2S\ O\ 4$)

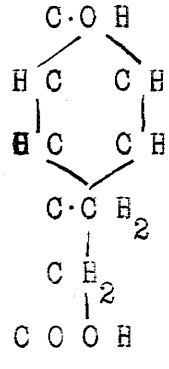
Conjugation with H2 S O4 occurs in the liver and if the amounts of aromatic bodies are large or the available $H_2S\ O_4$ scanty - conjugation occurs with d-glucuronic acid -beyond the small fraction always combined in this manner.

A fraction of Tyrosin or phenylalanine may possibly be converted to Benzoic Acid.

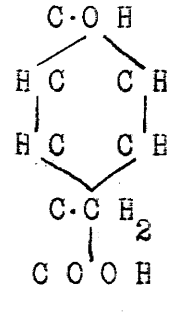
Tyrosin



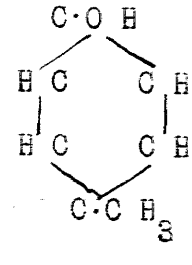
P-oxyphenyl-propionic acid.



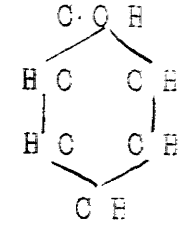
P-oxyphenyl acetic acid.



Para cresol



Phenol



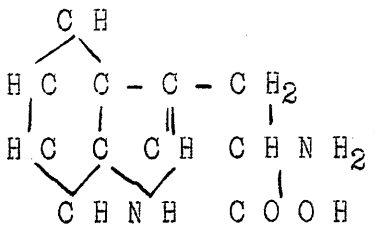
Phenylalanin.

Is converted to para cresol or phenol like tyrosin.

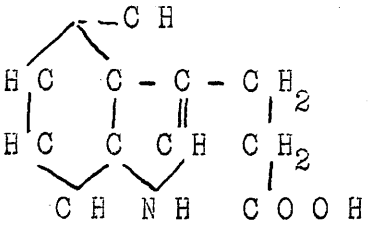
Tryptophane.

It is deaminated and the propionic acid formed oxidized to acetic acid which splits off and is burned and the indol oxidized to indoxyl, (the latter reaction occurring in the tissues). This is conjugated with H_2SO_4 (sometimes with d. glucuronic acid).

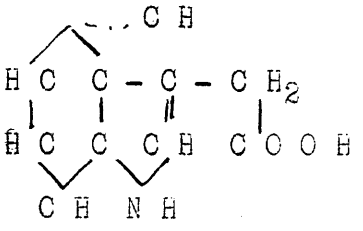
Tryptophan.



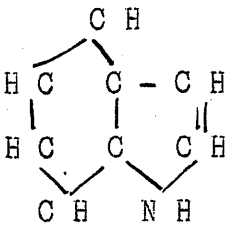
Indol propionic acid



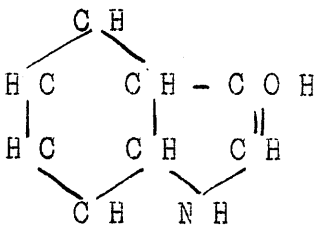
Indol acetic acid.



Indol.



Indoxyl.

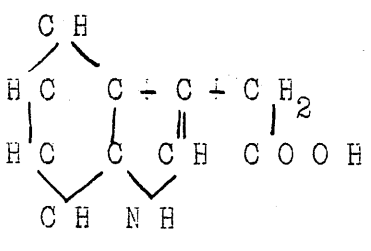


Indoxyl and Potassium Hydrogen Sulphate = Potassium -indoxyl sulphate and water

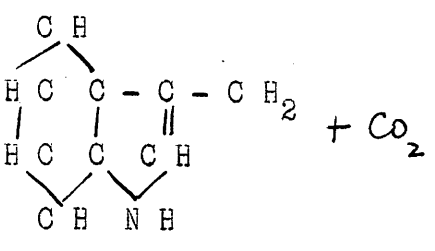
$$C_8H_7NO + SO_2\begin{matrix}OH\\OK\end{matrix} = SO_2\begin{matrix}O.C_8H_6N\\OK\end{matrix} + H_2O$$

The indol acetic acid by splitting off CO_2 - -methyl indol or skatol is derived.

Indolacetic acid



Skatol



All the aromatic bodies absorbed from the intestinal canal do not a appear in the urine - a portion is burned. Phenol and cresol are never in the body converted into indol and skatol. It may be queried whether it is possible for tryptophan to be formed from the combination of a pyrrol group with a benzene ring - or whether it may be got in bile or in the intestine as a result of catabolism of haematin.

Tyrosin and Phenylalanin may be converted to amines instead of being deaminated C O_2 being split off.

The composition and metabolism of the protein molecule having been considered - its ultimate dissociation may briefly be described as falling under the following headings:-

(1) Carbonic acid.

(2) Water,

(3) Sulphates.

(4) Urea.

(5) Creatinine.

The sulphur containing portions of this molecule will occupy our attention further.

Sulphur occurs in the urine in three forms.

1. Inorganic Sulphates.

2. Ethereal Sulphates.

3. Neutral Sulphur

A portion of sulphur is also eliminated by the cutaneous secretions (about 30 mgms. daily) and with the excreta of the alimentary canal (.2 - .3 grm daily), the latter being composed of

ingested inorganic salts

Sulphur compounds of the Bile

Sulphur contaning mucin of alimentary secretions

Sulphur from idigested or unresorbed protein of the diet(modified by bacterial action)

Sulphur of the bacterial bodies.

and sulphuretted hydrogen.

1. Inorganic Sulphates.

Inorganic Sulphates are derived from the oxidation of the protein molecule therefore their amount is an idex of Protein metabolism. The proportion of Nitrogen to Sulphuric Acid excreted is 5 to 1. They are derived almost entirely from the exogenous metabolism of food protein - and these depend on the nature of the diet.

The excretion of Inorganic Sulphates runs para passu with that of urea so that soon after the throwing off of the N H_2 group of the protein molecule, there must be a removal and oxidation of the greater part of the sulphur contained in the Cystine group.

2. Ethereal Sulphates.

These Sulphates are produced partly metabolically and partly as a result of the union of aromatic substances produced by intestinal putrefaction - with sulphuric acid. They are therefore not an absolute gauge of intestinal putrefaction.

They are excreted in varying quantities according to the extent of the decomposition processes which occur in the intestines. Under these processes the tryptophane produced in the pancreatic digestion of Proteins is converted into indol and skatol - which are absorbed and deprived of their poisonous properties by oxidation and conjugation with sulphuric acid to form the inocuous substances indoxyl and skatoxyl sulphates of the urine.

If putrefaction is increased the relative amount of conjugated Sulphates is increased - and if the putrefactive processes are abolished by administration of calomel or napthalene - the Ethereal Sulphates disappear from the urine.

3. Neutral Sulphur.

A small amount of unoxidized or neutral sulphur is excreted in the urine - this probably includes different bodies as sulpho cyanates and cystine.

Neutral sulphur undergoes no decrease during starvation - which fact suggests that this portion of the sulphur output of the organism may be connected with Tissue Metabolism.

The proportion of Ethereal Sulphates to Inorganic Sulphates is as 1 to 10

The conjugation of aromatic products with sulphates to form Ethereal Sulphates renders them more or less harmless. Indican is one of these conjugated aromatic bodies and being easily recognized from its colour reaction has been held to be an idex of intestinal putrefaction.

Lygdon Browne states[1] that"from simply getting this striking reaction we cannot conclude that we are dealing with a case of intestinal intoxication

[1] Physiological Principles in Treatment p. 220.

In the first place constant relationship between putrefaction intoxication could only hold if the aromatic bodies were themselves toxic or if pairing were a tax on the body. But even if it were so, we cannot judge of the total paired sulphates from the amount of indicanuria alone which only represents one of them. The time given for reabsorption will also be greatly influenced by the rate at which the contents are passing along the canal".

He suggests that " whether such substances do or do not exert their toxic effect depends largely on whether they are free or whether there is sufficient sulphate for them to combine with - in which state they are harmless, and is of opinion that the ratio $\frac{\text{Ethereal Sulphates}}{\text{Simple Sulphates}}$ gives a much surer indication of the existence or approach of an intoxication by aromatic bodies than we can possibly obtain by testing for indicanuria.

In support of this view may be quoted a case described by Sir A. E. Garrod (1) of a woman who had had carbolic dressings applied to an ulcer in the leg for a considerable time. He reported that she was on the verge of carboluria although the urine did not darken on standing. This statement was put to the test for the carbolic dressings were resumed with the result that the patient did have an attack of carboluria. His opinion was based on the observation that almost all the sulphates were in the form

(1) Transactions of the Pathological Society 1904 Vol LV p. 142
Quarterly Journal of Medicine vol. 1. p. 207.

of Ethereal Sulphates i. e. her power of neutralizing the toxic effects of phenol was taxed almost to the full. A little more and she was over the brink.

In the 5th Annual Report of the Cardiff City Mental Hospital (1912) Dr. Stanford writes "In collaboration with Dr. E. Barton White the action of several common intestinal bacteria on media containing indole has been studied. In no case was the production of any indigo forming substance observed, and this is an additional argument against the common assumption that indicanuria is necessarily connected with excessive intestinal putrefaction"

I have therefore taken in the present research - the ratio of Ethereal to Simple Sulphates as a guide to the condition of an existing toxaemia. In many cases this ratio has been worked out on samples of urine submitted for examination from twenty four hours collection. In most cases, however, the ratio has been worked out in samples of urine taken, before, during or after a period of convulsive seizures. In many cases as during periods of acute excitement or confusion - it was practically impossible for obvious reasons to collect all the urine passed in twenty-four hours. As however it was only a question of ratio - and not of total daily amount excreted - the

examination of samples other than 24 hourly specimens and has not in any way vitiated the correctness of the results obtained or inferences claimed. Coombe[1] has quoted a physiological variation in the daily excretion of Ethereal Sulphates and gives the following table :-

	gm.
At 8 a.m.	.06 per 1000
"12 noon	.027 "
" 8 p.m.	.147 "

as however most of the urines were collected about the same time during the day (early morning) and as ratios only have been studied, these variations need not be taken into account.

These observations have all been made on insane Epileptics and have been grouped under the following headings:-

(1) The urine taken during periods when the patient was either quite free from fits or comparatively free from fits.

(2) The urine taken during periods shortly before the onset of a series of convulsive attacks.

(3) The urine taken during the early stages of a series of convulsive attacks.

(4) The urine taken shortly after a series of convulsive attacks.

(5) The urine taken during periods of excitement and confusion. (the psychical equivalent of the convulsive period)

(6) The urine taken shortly after a period of confusion and excitement.

My object has been to ascertain whether the ratio of Ethereal to Simple Sulphates changed in any way during these various periods, if so in what

(1) Intestinal Intoxication (Combe).

way and was the change constant.

Twenty observations have been made under most of these headings - not necessarily on different cases - as some of the cases have been re-examined in order to corroborate previous results obtained.

In carrying out this examination the following method has been adopted:-

Estimation of Ether Sulphuric Acid.

(1) 100 c c. of urine taken and 100 c c of the following solution added and allowed to stand a short time (Saturated Solution of Barium Hydrate 2 vols)
(Saturated Solution of Barium Chloride 1 vol)

(2) Filter through close textured paper (100 c c of filtrate= 50 c c urine) acidify strongly with H C L and heat nearly to 100° c.

(3) Keep warm for 1 - 2 hrs then stand in cold 24 hours.

(4) Pass through a small ash free filter.

(5) Wash precipitate thoroughly with distilled water then alcohol.

(6) Dry and burn in Platinum crucible - ignite the residue, cool in dessicator and weigh.

Estimation of Sulphuric Acid.

(1) Dilute 50 c c. of urine with equal volume of Aqua Distil.

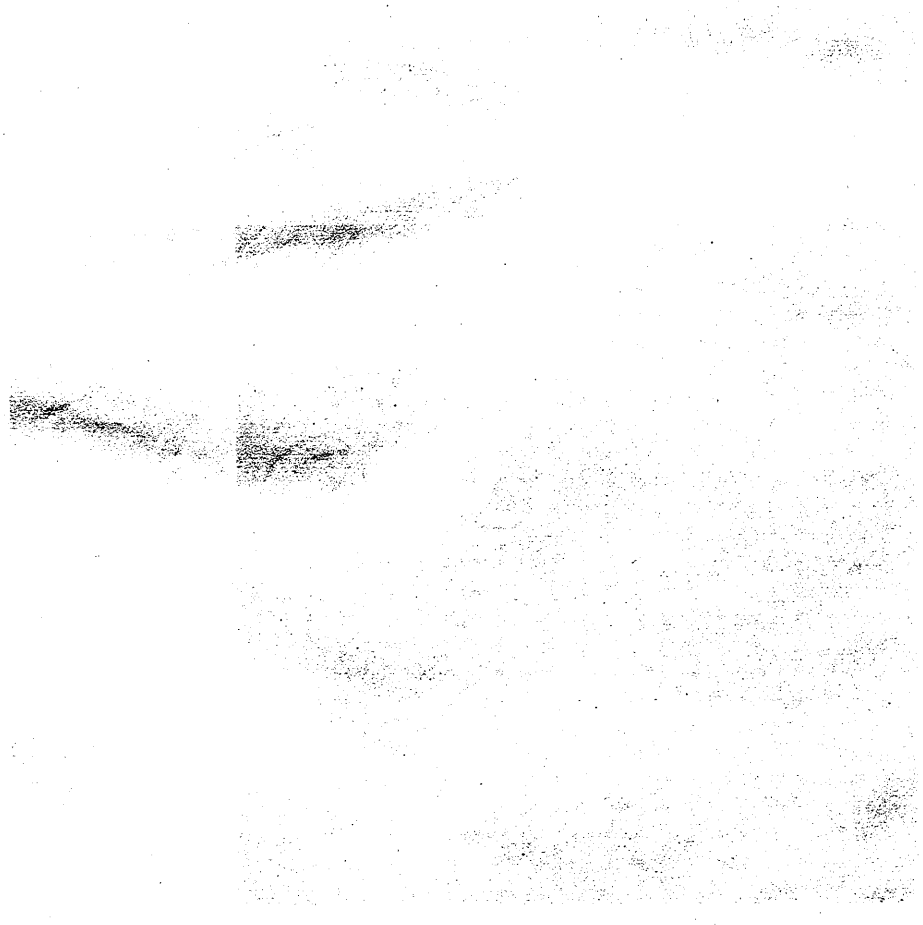
(2) Nearly boil and add B a C L_2 Solution (10%) in slight excess (add 10 c c H C L)

(3) Treat precipitate as above and weigh.

4. Subtract the weight of Ether Sulphuric Acid from this weight of total sulphuric acid and the result is the weight of inorganic sulphuric acid.

As regards the dietary of the cases examined:-this was a simple mixed diet and contained on average per diem - Proteids 2.6 ounces, Fats 1.4 ", Carbo-hydrates 12 " } Calculated free from water.

The figures given in the various analyses are in terms of Simple Barium Sulphate and Ethereal Barium Sulphate and have been left so and not reduced to terms of SO_3 as it was simply a question of ratio



Normal Periods

	Name	Age	Convulsive seizures	Simple Sulphates In 50c.c.urine	Ethereal Sulphates. In 50 c.c. urine.
1.	L. B.	22	Analysis taken in the middle of a period of at least one week's freedom from a convulsive attack and not immediately prior or subsequent to a period of convulsive attacks.	.210 gram.	.082 gram
2.	L. B.	22		.257	.063
3.	L. B.	22		.112	.062
4.	T. R.	60		.102	.070
5.	B. T.	28		.139	.051
6.	F. J.	30		.211	.057
7.	G. H.	28		.160	.056
8.	L. B.	22		.260	.049
9.	J. H.	24		.234	.032
10.	W. C.	33		.102	.060
11.	J. H.	24		.159	.094
12.	T. R.	60		.120	.069
13.	R. J. L.	15		.167	.069
14.	J. H.	24		.152	.068
15.	R. J. L.	15		.107	.059
16.	G. M.	32		.157	.035
17.	G. M.	32		.280	.050
18.	W. T. B.	50		.137	.060
19.	H. F.	36		.141	.058
20.	D. G.	28		.138	.051
			Average	.167	.059

2. Pre-convulsive Periods.

	Name	Age	Convulsive Attacks.	Simple Sulphates. In 50 c c Urine	Ethereal Sulphates. In 50 c c urine
1.	R. J. L.	15	The Urine taken for analysis	.078 gram.	.057 gram.
2.	G. M.	32	were in cases showing rest-	.202	.188
3.	R. J. L.	15	lessness, irritability,	.076	.080
4.	L. B.	22	quarrelsomeness, confusion of	.158	.066
5.	L. B.	22	thought, impulsiveness or	.058	.038
6.	C. C. H.	46	aggresiveness, violence or	.032	.040
7.	F. C.	45	unusual conduct (as uncontroll-	.041	.041
8.	F. H.	39	able laughter or eccentric	.068	.068
9.	R. J. L.	15	movements). Such mental condition	.086	.093
10.	W. C. M.	21	and conduct always occurred (in	,068	.044
11.	E. K.	52	the cases where urine was	.075	.050
12.	R. J. L.	15	examined) shortly before the	.052	.041
13.	R. J. L.	15	onset of the convulsive attacks	.068	.071
14.	J. H.	24	or series of attacks.	.142	.050
15.	J. H.	24		.060	.046
16.	W. T. B.	51		.070	.045
17.	G. M.	32		.179	.101
18.	T. R.	60		.091	.078
19.	A. D.	25		.087	.041
20.	G. B. A.	38		.093	.054
			Average	.1088	.064

Convulsive Periods

(Early stage)

Name	Age	Convulsions	Simple Sulphates In 50cc urine	Ethereal Sulphates In 50ccurine
1. R. J. L.	15	Analysis of Urine taken in	.078 gram.	.082 gram.
2. L. B.	22	early stage of the convulsive	.090	.080
3. T. R.	60	period extending as a rule	.109	.063
4. J. H.	24	over several days, convulsions	.110	.058
5. D. S. O'C	41	occurring irregularly over this	.119	.073
6. R. J. L.	15	period.	.110	.065
7. H. D.	43		.024	.018
8. R. H. R.	21		.135	.067
9. L. B.	22		.105	.043
10. R. J. L.	15		.089	.072
11. F. S.	48		.158	.103
12. W. C. M.	21		.163	.106
13. F. S.	48		.032	.041
14. L. B.	22		.046	.054
15. F. S.	48		.065	.040
16. W. F.	16		.204	.085
17. R. J. L.	15		.031	.028
18. H. D,	43		.029	.027
19. J. H.	24		.055	.056
20. J. H.	24		.134	.107
		Average	.094	.063

Post Convulsive Periods.

	Name	Age	Convulsive attacks	Simple Sulphates. In 50 c c urine.	Ethereal Sulphates. In 50 c c urine.
1.	R. J. L.	15	Analysis of urine taken at	.298	.060
2.	R. J. L.	15	the termination of a period	.212	.072
3.	L. B.	22	of convulsive attacks.	.308	.066
4.	L. B.	22		.326	.072
5.	R. H. R.	21		.304	.072
6.	T. R.	60		.177	.045
7.	D. S. O'C	41		.077	.061
8.	F. C.	45		.204	.086
9.	R. J. L.	15		.224	.072
10.	R. J. L.	15		.298	.060
11.	H. G. W.	44		.147	.047
12.	L. B.	22		.140	.048
13.	R. J. L.	15		.241	.053
14.	R. J. L.	15		.339	.065
15.	G. H.	28		.209	.047
16.	G. H.	28		.115	.087
17.	C. C. H.	26		.403	.063
18.	D. S. O'C	41		.103	.051
19.	R. J. L.	15		.101	.014
20	R. J. L.	15		.085	.063
21.	T. R.	60		.506	.117
22.	W. T. B.	32		.095	.064
23.	W. H. C.	26		.145	.050
24.	J. H.	24		.232	.054
25.	H. G. W.	44		.167	.041
26.	J. H.	24		.197	.056
27.	J. C.	18		.136	.050
28.	C. C. H.	26		.314	.060
			Average	.218	.060

5. Periods of Restlessness and excitement without convulsions.

Name	Age	Convulsions	Simple Sulphates In 50 c c urine	Ethereal Sulphates In 50 c c urine.
1. R. H. R.	21	Analysis taken of urine	.059	.068
2. G. M.	33		.048	.051
3. F. M.	33	whilst patient was restless,	.036	.036
4. G. M.	33	excited and confused. Such	.058	.064
5. G. M.	33		.048	.050
6. R. H. R.	21	mental condition lasting over	.099	.069
7. R. H. R.	21	a period of several days, and	.137	.067
8. D. S. O'C	41		.102	.050
9. W. T. G.	22	taking the place of convulsive	.109	.094
10. G. M.	33	attacks.	.055	.065
11. M. F.	42		.085	.062
12. J. H. E.	36		.203	.108
13. R. C.	40		.084	.040
14. W. T. G.	22		.056	.062
15. H. G. W.	44		.069	.052
16. G. H.	28		.215	.135
		Average	.089	.066

6. After Periods of Restlessness and Excitement.

Name.	Age.	Convulsions.	Simple Sulphates. In 50cc urine	Ethereal Sulphates, In 50 c c urine.
1. D. S. O'C	41	Analysis of Urine taken after periods of excitement, restlessness and confusion (without convulsive attacks)	.203	.064
2. W. T. B.	33		.208	.071
3. H. G. W.	44		.218	.084
4. T. R.	60		.159	.063
5. D. S. O'C	41		.202	.044
6. J. H. E.	36		.107	.045
7. F. C.	45		.308	.064
8. C. C. H.	46		.404	.060
9. W. H.	37		.140	.075
10. G. H.	28		.103	.057
11. M. F.	42		.126	.055
12. R. C.	40		.148	.044
		Average	.198	.060

The figures given in the various analyses are in terms of Simple Barium Sulphate and Ethereal Barium Sulphate and have been left so and not reduced to terms of $'S\ O_3$ as it was simply a question of ratio.

1. Normal periods - this represents urines taken in the middle of a period of at least a week's freedom from fits - such period not immediately preceeding or succeeding ; a period of numerous convulsions or prolonged excitement. In such periods the ratio of simple or preformed to ethereal sulphates has been found to work out at .167 to .059 (10 - 3.5) This shows a far higher proportion of ethereal sulphates to simple sulphates than in that given as normal generally i. e. 10 to 1.

The nearest approach to this latter ratio was .082 simple sulphates / .234 ethereal sulphates which occurred in a youth (J.H.) who had had no fits for five days previous to or nine days succeeding the analysis. The highest ratio was 10 to 7 in a man (T.R.) who was free from fits for four days previous to fourteen days succeeding the examination.

Considerable variations occur in analysis of the same patient - thus we get

L.B.	.082	.063	.062	.049	and	J.H.	.032	.094	.068	and	R.J.L.	.069	.059
	.210	.257	.112	.260			.234	.159	.152			.169	.107
T.R.	.070	.069	and	G.M.	.035	.050							
	.102	.120			.157	.280							

---

2. Periods before a number of fits.

The ratio of simple to ethereal sulphates here works out at 10 to ~~6.8.~~ 7.2 We thus see that on the approach of a fitty period the ratio of ethereal sulphates rises. The highest ratio of ethereal sulphates to simple sulphates is $\frac{.071}{.063}$ in the case of a youth (R.J.L. aged 17) who was subject to well marked periodical convulsive periods.

The lowest ratio of $\frac{.050}{.142}$ occurred in the case of (J.H.) and was taken three days before a convulsive period - during the early stages of which the ethereal sulphates exceeded the preformed in amount.

Variations in the same patient occur as follows:-

R. J. L. $\frac{.057}{.078}$ $\frac{.080}{.076}$ $\frac{.093}{.086}$ $\frac{.041}{.052}$ $\frac{.071}{.063}$; L.B. $\frac{.066}{.158}$ $\frac{.038}{.058}$; J.H. $\frac{.050}{.142}$ $\frac{.046}{.060}$

The low ratios in the case of L. B. and J. H. were in urines taken three and four days respectively before the onset of the convulsive period.

In several instances in R. J. L.'s case the ethereal sulphates were in excess of the simple sulphates pointing to an active toxic condition prevailing.

3. Periods during which convulsions were occurring more or less frequently (early stages)

The ratio of simple to ethereal sulphates works out at 10 - 6.7 that is to say the ethereal sulphates are a fraction less than in the preconvulsive

period. This shows that the ethereal sulphates have reached their highest intensity and are beginning to decline.

Variations in the examinations of the same case occur as follows:-

R.J.L.	.082	.065	.072	.028	L.B.	.080	.043	.054	F.S.	.103	.041	.040
	.078	.110	.089	.031		.090	.105	.046		.158	.032	.065

The case M F showing a ratio of $\frac{.085}{.204}$ was in a youth having a single fit almost daily and on light diet. The other examinations were carried out in cases having a periodic succession of convulsive seizures, As in the preconvulsive period several instances occur where the ethereal sulphates are in excess of the simple sulphates.

4. Periods after a series of Convulsions

The ratio here of simple to ethereal sulphates is as 10 to 2.7 the lowest of the whole series and the nearest approach to the normal standard of 10 to 1. The aromatic content is low probably because after a convulsive period the patient often consumes less food and at times has to be put on a milk diet. It suggests also that the acute stage of intoxication is passing away.

5. Periods of Restlessness and Excitement without Convulsions.

The ratio of simple to ethereal sulphates works out at 10 to 3.4. These cases showed much mental confusion - agitation and disorientation. Some were impulsive and many hallucinated and deluded. The average ethereal sulphate content is very high - the highest in the series and points to a

toxic condition prevailing.

6. After periods of excitement.

The ratio here of simple to ethereal sulphates is 10 - 3.1 and follows closely the ratio in periods after a series of convulsions.

Taking single patients and studying the ethereal sulphates eliminated in the different phases we get similar results to those obtained in the examination of a number of different cases

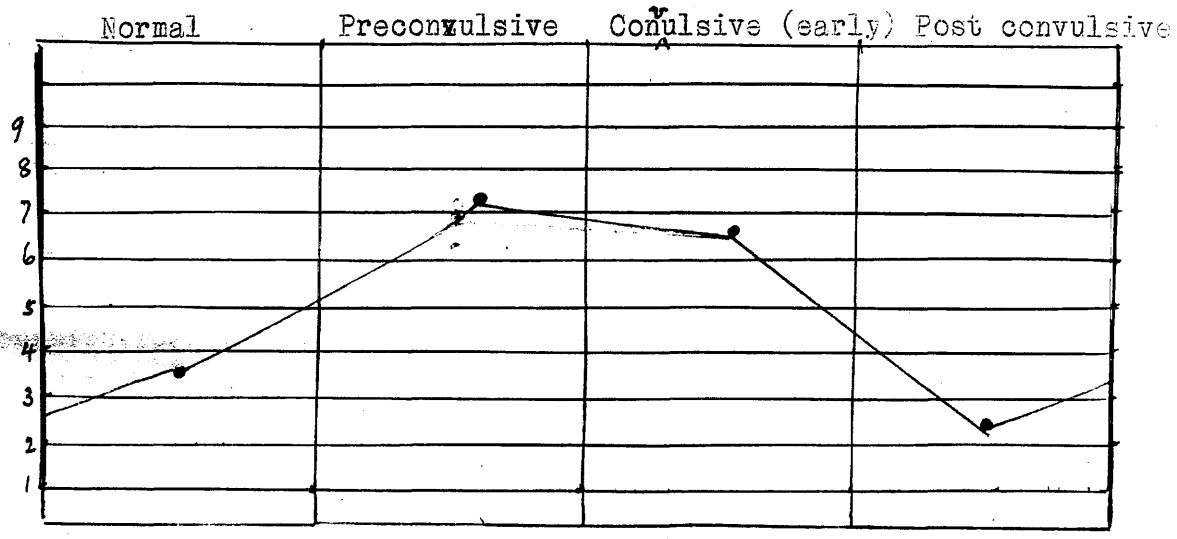
	J.H. Simple Sulphates In 50cc urine	J. H. Ethereal Sulphates In 50 cc urine	R.J.L. Simple Sulphates in 50 cc urine	R.J.L. Ethereal Sulphates in 50cc urine	T.R. Simple Sulphates in 50 cc urine	T.R. Ethereal Sulphates in 50cc urine	L.B. Simple Sulphates in 50 cc urine	L.B. Ethereal Sulphates in 50 cc urine
Normal Period	.159 grm .152	.094 gram .068	.167 grm .107	.069 grm .059	.120 grm .102	.069 grm .070	.260 grm .210	.049 grm .082
Before Convulsive Period	.142 .060	.050 .046	.063 .052	.071 .041	.091	.073 ~	.058 .158	.038 ~ .066 ~
In Convulsive periods (early stage)	.055 .134	.056 ~ .107 ~	.031 .089	.028 ~ .072 ~	.109	.063 ~	.105 .090	.048 ~ .080
After Convulsive periods	.232 .197	.054 ~ .056 ~	.101 .085	.014 ~ .063 ~	.506	.117 ~	.308 .140	.066 ~ .048 ~

Even in each period, examination gives results varying to a considerable extent - although taken on a whole they show a rise in the ethereal sulphate content before convulsive periods in the early convulsive periods and a decided fall after the convulsive period. There are slight exceptions to this rule, thus in the case of J. H. in the preconvulsive period we have

a ratio of .050/.142 and in the convulsive period it rises to .056/.065. The fall in the ratio after the convulsive period is well marked .117/.506 and this I have found to be the case in most examinations. Also L.B. shows a low Ethereal ratio in the preconvulsive + convulsive periods on one occasion - .066/.158 + .043/.105 respectively.

Apparently the high ratio of ethereal sulphates is present only in the early stage of the convulsive period - it does not occur in the later stages of a prolonged convulsive attack lasting off and on for some days.

A graphic representation of the rise and fall of the ethereal sulphates may thus be shown



With reference to the urinary analysis of cases having epileptic seizures at irregular times and not indefinite and well marked phases, the excretion of the sulphates has been varied and no certain conclusions could be drawn from the analytical results obtained.

We thus see that even in normal periods the ethereal sulphates are in excess of their normal ratio to simple sulphates and that the ratio of these ethereal sulphates increases as convulsive periods approach and reaches a maximum shortly before the convulsive period - falling to a

lower level than the epileptic normal after convulsive periods.

The question arises - does this constitute an intoxication ? It has been argued before that it does. It is not here maintained as a thesis that an alimentary toxaemia is the principal cause of convulsions - but it is held that given a weakened mental stability - whether congenital or acquired - then toxins of an irritating nature generated in the alimentary canal or elsewhere - will so to speak set fire to the train of powder that eventually produces the explosion, i. e. the convulsion. It is not maintained that the ethereal bodies conjugated with $S O_3$ are themselves very irritating and as such give rise to convulsions, (although in some constitutions they may prove irritants) but that a high content of ethereal sulphates points to putrefaction processes occurring in the alimentary canal parallelly with this production and that besides the tax on neutralization - toxins are produced of an irritating nature and these in all probability are direct nerve excitants. They may also act indirectly on the cortical nerve cells by producing vaso-motor spasm.

Of the substances formed by putrefactive processes in the alimentary canal - the following react deleteriously on the constitution :- (1)

ammonia (in excess), tyramine - histidine base - indolethylamine - agmatine - isoamylamine - } Putrescin + Cadaverin may be produced by putrefaction of Proteids in Intestinal Digestion (2) Roos discovered these substances in the urine in Enteritis.

Indol - skatol and sepsin. } putrefaction of Proteids in Intestinal Digestion (2) Roos discovered these substances in the urine in Enteritis.

(1) Alimentary Toxaemia (Dixon) p. 130.
(2). Garcia. Zeits. f. phys. ch. XVII p 568

An excess of ammonia or carbonic acid in the Portal vein may produce hepatic lesions (Rovighi)(4).

Joannovics produced an intoxication by administering ammonium carbonate by the stomach.
Krainsky showed that ammonium Carbammate was an essential irritant in many Cases of Epilepsy.

Tyramine is produced from Tyrosine by decarboxylation and is a poisonous substance. It is formed only by putrefaction.

Histidine base is poisonous and is produced by putrefactive germs from histidine.

Indolethylamine is produced from tryptophane by putrefactive processes and similarly agmatine is produced from arginine and Iso-amylamine from leucin and phenyl-ethylamine from phenylalanine. All of these products are more or less poisonous.

Indol and skatol are probably poisonous - cresols and phenols less so. Richards and Howland (1) demonstrated the possibility that defective oxidation of substances of this group may permit of intoxication. Iso-amylamine and para-hydroxy-phenyl-ethylamine act as pressor substances. (Barger and Walpole) and resemble adrenalin - but are more prolonged in their action.

Tyramine (2) acts when given by the mouth as well as hypodermically

Indolethylamine (3). when absorbed rapidly or in considerable amount excites the nervous system, producing clonic and tonic convulsions and vasomotor constriction with rise of blood pressure. It stimulates the muscular

(1). "Science" 1906 (24) 974.
(2). Laidlaw. Biochem. Journ. 1911 VI p. 141.
(3). ~~Journ. of Phys. 1910 XLI p. 318 or 1911 XLIII p. 182~~ Dale & Dixon Journ. of Phys. 1909 XXXIX p 25
(4). "Ricerche Sperimentali" Il Morgagni 1899 XLI (1) pp 449-64.

tissue of the arterioles (Laidlaw)

Histidine base[4] injected into animals produces vomiting, purging, salivation, laboured respiration from bronchiole occlusion and later collapse and light narcosis (Dale & Laidlaw).

Agmatine causes some constriction of plain muscle. Abelous found a pressor base in normal urine and named it "urohypertensine" and Barger and Walpole attributed this action to iso-amylamine.

Bain[3] found another pressor base in the urine - probably parahydroxy-phenylethylamine and is of opinion that such bases are retained in the body in cases of high blood pressure and have to do with its production.

Clairmont and Ranzi (1) found heat resistant toxic substances in the intestinal contents in ileus (experimental) and similar substances could be obtained by growing cultures of intestinal contents in bouillon

Magnus Alsleben[2] found in upper part of the small intestine of dogs (except when on milk diet) a very poisonous substance which kills rabbits by respiratory paralysis but which is inert when injected into the portal vein.

(1) Arch.Klin. Chir. 1904 (73) 696.

(2) Hofmeister's Beitr 1905 (6) 503

(3). Bain Lancet 1910 I.p. 1190 1911. I/p. 14

(4). Journ. of Physiol. 1910 XLI p 318 1911 XLIII p 182

Agostini showed that convulsions were determined by the accumulation of toxins in the blood. The toxity of the urine also increased before a convulsion and was in strict relationship to the gravity of the con-comitant gastro-intestinal disturbances. After a fit the urine was hypertoxic. Galanti and Savini showed that there was increased production of ethereal sulphates before a fit.

These are undoubtedly aromatic bodies which escape conjugation with S O_3 or Glycuronic acids and which are irritants and intoxicants.

The indican content of the urine does not render us great assistance as it is only one of the aromatic substances formed - is somewhat fugitive in its reaction and does not parallely increase and decrease with the etheral sulphate content. This I have found in frequent examination.

Indoxyl is derived from tryptophan only so that if the proteins ingested are poor in tryptophan the stools and the urine will leave a low indoxyl content, as putrefaction processes cannot form it from the products of digestion.

The question arises - granted the tryptophan ingested in the diet is a fixed quantity would the indican of the urine be an index of putrefaction of tryptophan in the intestine ? This would happen

if the absorption was always constant or if all of this substance was absorbed. A good absorption would give a well marked reaction and vice versa a poor absorption a faint reaction, the intestinal content being similar

Regarding the aromatic bodies generally - it is evident that those appearing in the urine conjugated with $H_2S O_4$ are not the only aromatic bodies in the urine. The p. oxy-phenyl propionic acid and p. oxy phenyl-acetic acid are present as simple salts in the urine in small amounts. Free volatile acids may be present and are always present in conjugation with glycuronic acid. Vegetables and fruits contain a considerable amount of aromatic bodies not excreted as ethereal sulphates.

It is believed also that certain aromatic bodies absorbed from the intestine are destroyed in the body and it has been suggested that the variations in the urinary aromatic bodies in different individuals might be due to differences in the power of combustion of aromatic bodies.

Again Variation in absorption of aromatic bodies may be due to different vital conditions of the mucous membrane of the intestine.

Intoxication The factors to be taken into consideration are:-

1. The rate of absorption and the quantitative production.
2. The bacterial content of the intestine.

3. The composition of the Diet.

4. The nature of the defences of the body.

The absorption rate being a vital process will vary with the individual. Excessive putrefaction will give rise to an increased production of aromatic bodies and a similar effect will be produced if the diet contains an excess of protein tyrosin and tryptophane. The natural defences include the liver and the ductless glands and will vary with the individual. (1) Richards and Howland have indicated the increased toxicity of indol when the oxidizing power of the liver is reduced and Herter and Wakemann have shown the power of the liver to combine indol and thus remove it from the circulation.

Some alkaloids may be destroyed in the alimentary canal by microorganisms others are converted into harmless substances.

The Phenols as before mentioned combine with Sulphuric Acid to form Sulphates which are quickly excreted. Benzoic and Salicylic acids unite with glycocoll and are thus excreted. Indol and skatol as previously stated are oxidized and combine with Sulphuric acid. Para hydroxy-phenyl-ethylamine is partly oxidized to para hydroxy-phenyl acetic acid and partly disappears untraced (Ewens and Laidlaw).

In Insane Epileptics we have various causes at work to assist in producing an alimentary toxaemia. Firstly most insane patients have defective teeth and swallow their food in gulps with little mastication - the result being that it is not broken into fine particles and the digestive juices are unable to adequately fulfil their metabolic function.

(1) Chemical Pathology. H.G. Wells.

The food undigested travels to the ileum and colon and on its way becomes pabulum for bacteria. Again constipation and a lowered state of vitality and nerve energy are potent factors in causing not only an increased formation of toxins but an increased absorption of them. Further active exercise is not the rule in the majority of such patients and this undoubtedly has some subtle influence on metabolism and the non combustion or indifferent elimination of toxic products.

A chronic toxaemia is liable to produce arterial changes - either the intima or media or both being affected. Gilbert and Lyon in 1889 showed that injections of bacteria and their toxins produced fibrocalcareous changes in animals.

Josué is 1903 showed that adrenalin injected into the veins of rabbits caused changes in the middle coats of the arteries and raised the blood pressure. Later experiments go to prove that pressor bases have a similar action.

Harvey[1] has noted arterio sclerotic changes from the administration of para-hydroxy-phenyl-ethylamine to rabbits by the mouth or intravenously and Etienne[2] has shown the same result by using isoamylamine. Changes occurred also in the kidneys.

If we compare the mental condition of many epileptics and neurasthenics

1. Journal of Path. Bact. 1911. XVI pgs.
2. Journ. de Physiol. et Path. Gen 1913 XV p. 103.

we find symptoms very similar - thus we get irritability often marked, incapacity for sustained mental or physical application - loss of concentration - quick temper - feebleness of purpose - easy fatiguability distractibility - lack of attention, restlessness, morbid fears, introspection and disinterest.

(In neurasthenia, a toxic condition frequently prevails and there is often marked indicanuria and excessive production of ethereal sulphates.) An improvement in these symptoms is brought about frequently by antiseptic purgation - a change of diet - both as regards quantity and quality - attention to mastication and physical exercise short of exhaustion.

(The administration of indol to man in large quantities is known to give rise to symptoms similar to those met with in many cases of epilepsy and neurasthenia.)

Leucocytosis.

With regard to the blood count - in the few cases I have examined I have found a decided increase in the number of white cells in early periods of excitement and convulsions pointing to a toxic condition of the blood.

To sum up - we have in many cases of epilepsy with insanity - definite phases in the disease; thus there are what may be termed

"normal periods" where convulsive attacks are few and the mind ~~is~~ clear fairly clear and rational. There are also preconvulsive periods and convulsive periods where excitement and confusion prevail as a rule and post convulsive periods of calm generally - although restlessness may occur and irrational conduct at such times.

In these different periods the ratio of ethereal to simple sulphates excreted in the urine varies. An increase in the ethereal ratio is noticed in the preconvulsive and early confusional periods and this it has been suggested points to a toxic condition prevailing in the system - poisonous products being elaborated in the Alimentary Canal which react on the nervous system and body generally in a deleterious way, and which may determine the onset of the convulsive state or its psychic equivalent.

F. E. Shaw.
30/6/14.

BIBLIOGRAPHY.

The Protein element in Nutrition - D. Mc Cay,

Alimentary Toxaemia, its causes, cosequences and treatment (From the Proceedings of the Royal Society of Medicine 1913 vol vi)

The Prolongation of Life - Metchnikoff.

Chemical Pathology - H. G. Wells.

Physiological Principles in Treatment - Langdon Brown.

Food and the Principles of Dietetics - Robert Hutchinson.

Handbook of Physiology - W. D. Halliburton.

Principles of Human Physiology - Starling.

Digestion and Metabolism
(The Physiological and Pathological Chemistry of Nutrition) - A.E.Taylor.

Practical Uranalysis and Urinary Diagnosis - Purdy.

Text Book of Physiological Chemistry - O. Hammersten.

Auto-intoxication and Disintoxication - G. Guelpa.

The Physiology of Protein Metabolism - E. P. Cathcart.

The Chemical Consitution of the Proteins - R.H.A. Plimmer.

The General Characteristics of the Proteins (Pt. 1 and Pt. 2) - S.B.Schryver

Simple Natural Bases - G. Barger.

Intestinal Auto-intoxication - A. Combe
Physiological and Pathological Chemistry - Bunge and Starling.
Metabolism and Practical Medicine - L. Von Moorden.
The Nutrition of Man - Russell H. Chittenden.
Modern Theories of Diet - Alexander Bryce.
The Physiology and Pathology of the urine - Dixon Mann.
The Book of Diet - Chalmers Watson.
Osler's system of Medicine.
New York Medical Journal 1898 vol. 68 (Herter)
Pathology - Ford Robertson.
Epilepsy - Aldren Turner.