established between the adjacent aspects of the small and large bowel. The objection to this method was that, however securely the ends of these portions of intestine were fastened down, they both dilated and formed sacs, that which projected from the ileum being considerably larger than that from the pelvic colon. This was not limited to my junctions, since I found that the same occurred in patients of surgeons who, as I knew, were very skilful operators. The accumulation of fæcal material, in the ileal cul-de-sac especially, soon becomes a source of great discomfort, and calls for treatment. For a long period I employed an end-to-side anastomosis, closing the pelvic colon and introducing the end of the ileum into an aperture in its side. This was generally very effective. I occasionally came across cases in which obstruction occurred at the junction on the removal of the tube. This obstruction did not always take place at once, but perhaps after a considerable interval; and again, it was not always persistent, but frequently intermittent. It seemed to me that this control of the ileal effluent resulted from some twisting of the bowel at the junction, and in order to obviate its occurrence I employed the end-to-end method. This last has afforded me complete satisfaction, and has freed me from the anxiety associated with the end-to-side junction.

BACTERIAL ACTIVITY IN THE ALIMENTARY TRACT.*

By N. MUTCH, LONDON.

In tracing the distribution of the aerobic bacteria of the alimentary tract in healthy adults, a moderately varied and luxuriant flora is met with in the mouth and stomach; the duodenum, jejunum, and most of the ileum are relatively sterile; a few bacteria are found in the lowest coils of the ileum, whilst the colon teems with innumerable organisms. There would seem to be a continual inflow of vegetable life through the mouth, a constant destruction in the stomach, and a studied encouragement of growth in the colon. The bacteria of the duodenum and jejunum probably represent the surplus which has escaped destruction in the stomach. Those of the ileum are the resultant of an ascending infection from the colon and the remnants of the inflowing stream from above.

Apparently the ideal which our vital mechanisms strive to attain is sterility of the alimentary tract above the ileocæcal valve, with very free bacterial growth below that barrier. The reason for this is not far to seek. The upper portions of the intestinal tube are laden with food products, useful alike for human and bacterial life. The presence of many organisms in these parts would result, not only in much waste, but in the production of highly poisonous modifications of our food materials, such as amines and ptomaines. On the other hand, although the colon can absorb sugar and proteolytic products¹ as well as water and salts, normally it is given very small opportunity of

* The expense of these researches was in part defrayed by a grant from the British Medical Association.

exercising this function. Mere traces of absorbable carbohydrates and amino-acids pass the ileocæcal valve, their loss is inconsiderable, and it is most important that toxic modifications should not be produced. A luxuriant colonic flora is therefore provided, to ensure their rapid destruction into relatively innocuous bodies such as phenol, ammonia, water, carbon dioxide, and hydrogen, whilst being stored up for daily evacuation.

To put the matter briefly, the upper alimentary tract is specialized for aseptic absorption of food, and the colon for the bacterial destruction of residues. It is conceivable that disease may arise from infection of the lumen of the upper alimentary tract, with the generation of poisonous decomposition-products; or from infection through the walls of the alimentary canal, with discharge of bacterial toxins into the circulation.

BACTERIAL DECOMPOSITION IN THE ALIMENTARY TRACT.

The process of food decomposition by bacteria is favoured by increase in the number of bacteria present, and by delay in the passage of food through the infected area. In the abdomen as elsewhere, delay and infection are intimately related to each other, and abnormal delay suggests heightened infection. In surveying the alimentary tract from the point of view of its mechanics, it will be seen that, in health, chyme is delayed at three points—in the stomach, in the lower ileum, and in the colon. In disease, delay may be increased in any or all of these localities, and also produced in the duodenum by the development of an abnormal fourth barrier at the duodeno-jejunal flexure.

Decomposition in the Stomach.—This is dominated by the abundance of carbohydrate present and the concentration of the hydrochloric acid in the gastric secretion, and unless the acidity is extremely diminished, only a limited variety of organisms can flourish. Even with marked hypo-acidity, gastric stasis is a necessary adjunct for free bacterial action. Amongst the organisms best adapted for growth in moderately acid media are the *B. acidophilus* of Moro, and yeasts. Both of these organisms can live in a medium which is acid to Congo Red, and both ferment carbohydrates with avidity, the latter producing gas and the former lactic acid. Hypo-acidity and motor disability are found in most cases of gastric carcinoma, but they occur also in the simpler cases of intestinal stasis, in which neither ulcers nor cancers are present.

Whenever these conditions are found in conjunction with each other, gastric fermentation proceeds freely—e.g., J. J.'s gastric secretion contained 0·076 per cent active hydrochloric acid; his stomach was not quite empty in six hours. He experienced much flatulence and heartburn. Organic acids were present in his gastric contents. Whereas G. S. had 0·301 per cent of active hydrochloric acid, and his stomach was empty in four hours. He was not troubled with flatulence or heartburn, and no organic acids were found in the stomach contents. Both patients suffered from marked colonic stasis, and in neither was any ulceration or malignant disease of the stomach or duodenum found at operation. J. J., showing hypo-acidity and gastric stasis, suffered from symptoms of decomposition in the stomach. G. S., showing hyperacidity and normal motor functions, was free from any such discomforts.

Decomposition in the Duodenum.—It is most unlikely that any appreciable bacterial decomposition takes place in the normal duodenum, because the transit of food through its lumen is rapid. In constipation, however, there is very frequently marked stasis of the duodenal contents, and from such duodenums pathogenic bacteria can be cultivated. This delay and consequent dilatation are part of a general stagnation in the stomach and duodenum, and are not usually associated with rapid emptying of the stomach, as was at one time suggested. The rate of stomach evacuation was studied in twelve consecutive cases of marked duodenal dilatation. The criteria of such dilatation were ocular demonstration by laparotomy, and orthodiagraphic measurement. Only those duodenums were considered in which the descending limb measured 4 in. or more.

TIME OF EMPTYING OF STOMACH IN DUODENAL DILATATION.

PATIENT	OPERATIVE FINDINGS	X-RAY MEASUREMENTS OF DESCENDING LIMB	TIME FOR STOMACH TO EMPTY
R. J.	Dilatation moderate	..	> 8 hours
K. L.	.. extreme	..	> 9 "
P. S.	.. extreme	..	> 8½ "
A. R.	.. extreme	..	> 8 "
C. M.	.. moderate	..	> 5 "
A. H.	.. moderate	..	> 4½ "
A. B.	.. moderate	4 in.	> 8 "
D. P.	.. moderate	4 in.	> 8½ "
K. S.		4 in.	> 5 "
M. K.		5 in.	> 3 "
J. F.		4½ in.	> 4 "
A. S.		5 in.	> 5 "

It will be seen that the stomach was empty in less than four hours in one case only, and that the average time of emptying was more than six hours. Extreme duodenal dilatation is therefore usually associated with marked gastric stasis. The probable teleological explanation of the phenomenon is, that delay at the upper end of the alimentary tube is nature's remedy for a greater accumulation of food in the lower ileum than that portion of the canal can deal with at the moment.

The importance of this means of regulating the inflow of chyme into the jejunum is illustrated by the case of M. B., age 26, who suffered from constipation, with marked ileal delay of about fourteen hours' duration, gastric delay of six hours, and a gastric ulcer not producing pyloric stenosis. Gastro-jejunostomy was performed, thereby overcoming gastric and duodenal stasis, but depriving the ileum of its means of protection against overfilling. When examined six months later, bismuth poured rapidly through the hole in the bottom of the stomach and collected in the lower ileum, where, by reason of its weight, it so aggravated the ileal delay that a large mass of bismuth failed to enter the cæcum till after the 96th hour (*Fig. 326*). On the seventh day the ileum was empty, and all the bismuth was in the colon. Even with the aid

of liquid paraffin, ileal delay was greater than fifty hours, although less than seventy-four hours. The actual mechanism of production of many cases of duodenal dilatation is kinking at the duodenojejunal flexure, brought about by the heavy pull, through gravity, of accumulated chyme in the lower ileum.

FIG. 326.—M. B. Six months after gastrojejunostomy. The photograph was taken ninety-six hours after a bismuth meal. Note the extreme ileal stasis.

These facts are clearly proved by the following cases, in which laparotomy was performed :—

A.—FIVE CONSECUTIVE CONSTIPATED PATIENTS WITH ILEAL DELAY GREATER THAN TEN HOURS.

PATIENT	DUODENAL DILATATION*
A. A.	Definite = +
M. W.	Definite = +
A. P.	Marked = 2+
H. S.	Marked = 2+
D. M.	Definite = +

Average measurement of dilatation = 1·4.

B.—FIVE CONSECUTIVE CONSTIPATED PATIENTS IN WHOM ILEAL DELAY WAS VERY SLIGHT, OR ABSENT.

PATIENT	DUODENAL DILATATION
R. G.	Doubtful = (+)
T. G.	Doubtful = (+)
G. W.	Definite = +
F. J.	Absent = —
E. T.	Definite = +

Average measurement of dilatation = 0·6.

* Throughout this paper an extreme condition is denoted by 3 +, a very marked one by 2 +, a definite one by +, a doubtful one by (+). This method supplies measurements which ignore small differences, and are therefore uninfluenced by small experimental errors.

It is evident that duodenal dilatation is intimately associated with ileal stasis, and the process of its production can be seen in operation in the case of E. B., a man, age 33, who complained of epigastric pain coming on about three hours after meals. It was the characteristic 'hunger' pain which often occurs with duodenal obstruction. A bismuth meal was given, and although the orthodiagraphic measurement of the vertical limb of the duodenum was $4\frac{1}{2}$ in., there was no pronounced distention, and bismuth readily entered the jejunum. In other words, the duodenum was large from previous obstruction, but obstruction was not actually present at the time of examination. He was

next seen three hours later, during a typical attack of pain. The duodenum was now distended (*Fig. 327*), and no bismuth was seen to enter the jejunum during ten minutes' observation. Examination of the rest of the abdomen revealed the immediate cause of obstruction—the greater part of the bismuth having now collected in the pelvis in the lower coils of ileum, where, by reason of its weight, it was acutely kinking the duodeno-jejunal flexure. From the foregoing data it is evident that duodenal stasis is most frequently found in conjunction with gastric and ileal stasis, and evidence of chronic duodenal infection should first be sought in patients presenting these conditions. The alkaline reaction of the duodenal chyme supplies a medium favourable to the growth of organisms which escape the sterilizing influence of the stomach, or which have ascended from the lower parts of the alimentary tract. Duodenal delay, hypochlorhydria, gastric stasis, and infection of the small intestine, occurring together, provide the conditions most favourable

FIG. 327.—E. B. Duodenum distended with bismuth during an attack of 'hunger' pain.

to the growth of bacteria in the duodenum.

Very commonly the subjects of constipation present a localized area of tenderness near the middle line, about $1\frac{1}{2}$ in. above the umbilicus. It is usually very pronounced when duodenal or gastric ulceration has supervened, but is more frequently present without such complications. It is uninfluenced by the position of the patient. It rarely corresponds with the surface-marking of the pylorus, which varies greatly according to the posture of the patient. The area of tenderness does, however, correspond accurately with the third part of the duodenum, which occupies a very constant position in all patients, and which does not drop appreciably in the erect attitude. *Fig. 328* demonstrates this point. Before the *x*-ray examination was made, the lower metal disc marked U was placed over the umbilicus and the upper one over

the area of maximum tenderness. The photograph was taken with the patient lying down. In the erect attitude the point of tenderness and the duodenum remained in the same position as before, but there was great ptosis of the pylorus. It is much easier to satisfy oneself that the duodenum and not the pylorus is tender, by abdominal palpation, aided by *x* rays and a fluorescent screen. Operative findings correlate this tenderness with duodenal dilatation. Out of seven consecutive laparotomies on patients with marked epigastric tenderness, pyloric ulceration was found in one only; in every case the duodenum was dilated, and in three this dilatation was extreme.

Consideration of the case of F. W. will show that pathogenic organisms may occur in the duodenum in disease. The patient, a man, age 29, suffered from cutaneous pigmentation, sweating, and anæmia, which had commenced six months previously and gradually increased in severity. When seen, his cutaneous discoloration was great, and suggestive of Addison's disease; but his blood-pressure was 125 mm. Hg. His hæmoglobin was 50 per cent; his red-count, 2,380,000; colour index, 1; white-count, 10,800; differential-count: polymorphonuclears 48 per cent, lymphocytes 47 per cent, hyalines 3 per cent, eosinophils 2 per cent. No abnormal white cells were found. The red corpuscles were round, even in size, and no nucleated forms were seen: that is to say, his

blood presented the picture of a severe secondary anæmia, with a relative lymphocytosis. His heart was slightly enlarged, and a loud hæmic bruit was heard. The urine contained a moderate amount of indoxyl, and much indolacetic acid. On *x*-ray examination there was pronounced ileal and colonic stasis. Laparotomy was performed, and some of the chyme withdrawn from the dilated duodenum. Plate cultivations were made, and a profuse and pure growth was obtained of a long-chained, Gram-positive, hæmolysin-producing streptococcus, which was probably responsible for the severe anæmia from which the man was suffering.

FIG. 328.—Shows the area of epigastric tenderness over the third part of the duodenum. P, Pylorus. D1, 2, and 3, Duodenum, parts 1, 2, and 3 respectively.

To recapitulate the facts just brought forward in connection with duodenal stasis:—

1. It is usually associated with ileal stasis, and is most marked when the lower ileum is distended with food.
2. It is usually associated with gastric stasis.
3. It gives rise to a localized tender area in the epigastrium.
4. It may be associated with duodenal infection.

In the present state of our knowledge it is impossible to differentiate between food poisons produced in the duodenal lumen and bacterial toxins produced in the walls of the canal.

Decomposition in the Ileum.—It is admitted by all who have given attention to the subject that in disease the lower coils of ileum frequently contain micro-organisms. It is easily proved by making cultures from ileal chyme removed at operation. That a few organisms occur in these parts of the intestinal tube in health is probable, but as yet lacks direct proof. There is, however, no doubt that in constipation the ileal flora is often immeasurably richer than in health, and that bacterial decomposition of the products of proteolysis gives rise to adverse symptoms in patients suffering from intestinal stasis. Most striking proof of these statements is made possible by the variations in ileal infection found in different subjects. For the moment it will suffice to mention two facts, and then enter on the more detailed discussion.

1. The degree of infection of the ileum with coliform bacilli varies directly as the degree of ileal stasis.

2. Constipated patients with subnormal blood-pressures harbour *B. aminophilus* in their ileums; other constipated patients do not do so.

The relative frequency with which various aerobic organisms can be cultivated from one platinum-loopful of diluted ileal contents (dilution 1–50) is: Coliform bacilli, 86 per cent; *B. acidophilus*, 68 per cent; *Streptococcus brevis*, 57 per cent; *B. aminophilus*, 36 per cent; yeast, 28 per cent; *Streptococcus longus*, 18 per cent; *B. proteus*, 6 per cent.

From consideration of a large number of cases it has been possible to detect the following factors which influence the coliform infection of the ileum.

A.—The degree of infection is proportional to the ileal stasis.*

The technique followed in all bismuth examinations was that 4 ozs. of bismuth oxycarbonate were given shortly after a meal, and no food was allowed until the stomach was empty.

Ileal delay:—

A trace of bismuth in the ileum at 8½ hours = ileal delay (+)			
A definite collection present	8½ to 9	„ = ditto	+
Ditto ditto	9 to 24	„ = ditto	2+
Ditto ditto	more than 24	„ = ditto	3+

In 5 consecutive cases of extreme ileal infection the average ileal

* I am indebted to Dr. J. Eyre for some of the quantitative counts of coliform and streptococcal organisms made use of in this paper.

delay was 1·6. (Plates overgrown with innumerable colonies of coliform organisms):—

PATIENT	ILEAL DELAY	
E. D.		+
B. M.		+
H. S.		2+
C. F.		+
E. L.		2+

Average measure of delay = 1·6.

In 8 consecutive cases of slight ileal infection the average delay was 0·6. (From 1 to 20 colonies appeared on the plates) :—

PATIENT	ILEAL DELAY	
G. W.		(+)
D. S.		—
D. M.		2+
C. J.		+
P. G.		+
H. E.		+
F. J.		—
A. A.		—

Average measure of delay = 0·6.

B.—The ileal kink acts as a protective barrier against ascending infection from the colon.

Cultivations were made on nutrose agar plates from one loopful of diluted ileal contents. Dilution was 1–50.

Coliform infection :—

Innumerable colonies =	3+	100 to 5 colonies =	+
500 to 100 „ =	2+	5 to 1 „ =	(+)

In 10 cases of marked ileal kink, the average measure of coliform infection was 0·75.

In 10 cases without ileal kink, the average measure of infection was 1·7.

Considering the data from another standpoint. In 6 cases of extreme coliform infection of the ileum, a definite ileal kink was present in 17 per cent. In 10 constipated patients with relatively slight coliform infection, a definite ileal kink was present in 90 per cent.

This protective effect of the ileal kink is not due to concurrent alterations in ileal stasis, because the average ileal delay of 12 consecutive constipated patients with marked ileal kinks was equal to the average delay in 12 consecutive constipated patients who had no ileal kink.

C.—The coliform infection varies directly as the duodenal dilatation.

This is a natural corollary to the fact that duodenal dilatation varies directly with the ileal stasis. In 6 cases of extreme coliform infection of the ileum, the average duodenal dilatation = 1·7. In 11 cases of relatively slight coliform infection, the average duodenal dilatation = 0·8.

*D.—The coliform infection is uninfluenced by the acidity of the stomach.**

If, as is probable, the coliform infection ascends from the large bowel, it

* For all examinations of stomach contents mentioned in this paper I am indebted to Mr. J. H. Ryffel, in conjunction with whom a more detailed and extensive analysis of results will be published later.

would seem unlikely that the gastric secretion could influence it in any way. The following figures justify this conjecture.

PATIENT	ACTIVE HYDROCHLORIC ACID		COLIFORM INFECTION	
B. M.	0.208 per cent	0.2 to 0.3 per cent	3+	Average measure of infection = 1.7.
G. S.	0.301 per cent		+	
M. L.	0.298 per cent		+	
E. D.	0.127 per cent	0.1 to 0.2 per cent	3+	Average = 1.7.
H. S.	0.184 per cent		3+	
D. S.	0.119 per cent		+	
D. M.	0.142 per cent		+	
A. E.	0.107 per cent		(+)	
D. B.	0.174 per cent		2+	
L. S.	0.086 per cent	0 to 0.1 per cent	3+	Average = 1.8.
F. J.	0.076 per cent		(+)	

Or, presenting the data in another way:—

In 5 cases of extreme coliform infection of the ileum, the average secretion of active hydrochloric acid = 0.15 per cent.

In 6 constipated patients with relatively slight infection, the average hydrochloric acid = 0.17 per cent.

The changes which may be induced in the lower products of proteolysis by intestinal bacteria are remarkable in that the toxicity of the resulting compounds varies very greatly. Probably in many cases highly poisonous substances are first formed by simple alterations in the structure of the useful nitrogenous products of enzyme action, and are subsequently changed into simpler innocuous but useless products by further bacterial action. For example:—

1. Useful tyrosin is first changed to highly poisonous hydroxyphenylethylamine, and ultimately becomes relatively innocuous phenol. In normal intestines most of the tyrosin is absorbed unchanged, whilst the residue passes rapidly into the colon and is destroyed:—

2. β -iminazolyethylamine is formed from histidin:—

3. Indolethylamine is formed from tryptophane :—

In the colon, where bacteria are present in billions, and the work of destruction can be taken up by relay after relay of organisms, relatively innocuous end-products arise. The highly toxic intermediate bodies are to be sought for where selected bacteria, not too numerous and not too versatile in their chemical potentialities, come into contact with the products of proteolysis.

The chyme in the lower end of the ileum is fluid, and consists of products of digestion, bile pigments, stercobilin, and ferments, dissolved in an almost neutral isotonic solution of sodium chloride and sodium carbonate. Experimental fistulæ in dogs show that 6 per cent of absorbable food reaches the cæcum. This is composed entirely of the simplest products of digestion, including traces of tyrosin, histidin, arginin, lysin, leucin, alanin, and aspartic acid.

The author has carefully examined the colon and lower portions of the ileum removed by Sir Arbuthnot Lane at operation on fifty occasions, and has noted the following points. Although the whole abdomen of constipated patients emits a fæcal odour, great differences can be observed between the offensiveness of the various portions of the intestinal canal, and the ileocæcal valve forms a great dividing line. If the lumen of the ileum is opened up by a longitudinal incision, and its contents exposed as far as a point 3 to 4 mm. from the cæcal aspect of the ileocæcal valve, the odour emitted is extremely faint; but immediately after the valve has been cut through completely, the usual nauseating vapours of fæcal matter become urgently obvious. It is quite evident that the contents of the cæcum do not usually regurgitate through the ileocæcal valve. This was demonstrated more completely still by bacteriological methods. Immediately after the abdominal wall had been opened at operation, a ligature was tied round the ileocæcal junction. Swabs were subsequently taken from the cæcum and lowest portion of the ileum. From the former, most luxuriant cultures were obtained; from the latter, comparatively slight growth. These observations dispose conclusively of the contention which Adami has from time to time put forward, that bacterial activity reaches a maximum in the lower ileum. The majority of the bacteria in the fæces may indeed be dead; but the number of living bacteria in 1 c.c. of cæcal contents is so immeasurably greater than the number in 1 c.c. of ileal contents taken 1 cm. higher up the alimentary tract, as to convince one of the

relative sterility of the small intestine. On several occasions a portion of ileum four or five feet in length was removed, and cultures were made from its contents at various points, with similar results in all cases. For example, in the case of S. K., age 40, with lifelong constipation, on whom a colectomy was done in March, 1914, the results were as follows :—

SITE		CHARACTER OF GROWTH	NUMBER OF COLONIES
Cæcum		Very free growth of streptococci and <i>B. coli</i> after 24 hours	= immeasurable
Ileum at the valve	..	Moderate growth	.. = 50
„ 10 cm. above the valve		ditto	.. = 20
„ 20 cm. ditto		Slight growth	.. = 1
„ 30 cm. ditto		Very slight growth	.. = 0
„ 40 cm. ditto		ditto	.. = 0
„ 50 cm. ditto		ditto	.. = 0
„ 60 cm. ditto		ditto	.. = 0
„ 70 cm. ditto		ditto	.. = 0

A few *B. coli* could be detected in these situations by working with larger volumes of chyme.

From these results it is evident that not only does the ileocæcal valve prevent gross regurgitation, but it also acts as a very efficient barrier against bacterial invasion of the ileum. Whether this function is dependent solely on mechanical prevention, or is aided by some bactericidal action, remains to be investigated. It would appear also, that the bacteria which live in the lowest portions of the ileum in constipation, very rapidly diminish in number as the distance from the cæcum increases.

Examination of the chyme points to similar conclusions. The volume obtained was always small, because of the routine starvation before operation. The reaction in all cases was amphoteric or faintly alkaline to litmus paper as far as the ileocæcal valve. In consistency it varied from fluid which could be poured from vessel to vessel, to small, formed, pultaceous masses of pale brown, almost odourless, matter. This semi-solid matter suggested that considerable absorption of water had taken place from the ileum; but it was not so common as the fluid chyme which was found in presence of, and in absence of, Lane's ileal kink. The colour was sometimes green, but usually yellow and brown. In the case already cited, a rapid transition in colour was seen from brown at the ileocæcal valve to bright yellow 20 cm. away from the valve. Chemical examination showed that in all portions, both bile pigments and stercobilin were present in large amounts. Near the valve the proportion of stercobilin to bile pigment was greatly in excess of that found in normal sterile bile, indicating considerable bacterial action; whilst 20 cm. higher up the ileum, the relationships of the pigments were indistinguishable from those in the gall-bladder. A similar condition was found in many other patients, and in no case was much stercobilin found at a distance greater than 10 cm. above the ileocæcal valve.

The end of the ileum in constipated subjects would appear from the foregoing discussion to be singularly well adapted for the production of intermediate bodies of bacterial action. The exact nature of the toxins elaborated depends upon the organisms present, and may vary widely in different patients. The evidence that such decomposition actually occurs may now be examined.

Urine probably contains from time to time many substances whose presence is due to bacterial decomposition in the alimentary tract. Those

of simple structure, such as phenol, may arise during the extensive disintegration of food residues in the colon, but the more complicated ones must be the resultants of restricted bacterial action in localities where proteolytic products are still unabsorbed. Tryptophane derivatives are often found in the form of

These bodies occur together or separately. Either may be formed by the action of coliform organisms on tryptophane; but the fact that pure cases of indolacetic urine and pure cases of indicanuria are met with, makes it probable that a separate strain of organism is responsible for the production of each substance. The interest of this speculation lies in the close relationship between indolacetic acid and the pressor body indolethylamine,

and in the fact that indolethylamine entering by the alimentary tract appears in the urine as indolacetic acid. Recently, I have isolated, from the urine of a patient with intestinal stasis, a tyrosin derivative, parahydroxyphenylacetic acid, ,

in a pure crystalline form.² This body is closely related to hydroxyphenylethylamine, , whose

pressor effect is so marked that it is sold by a well-known firm of chemists for therapeutic uses in 20 mg. doses. Hydroxyphenylacetic acid is easily detected by applying Millon's test to an ethereal extract of acidulated urine. I have now found it present in large amounts in three or four patients, and in small amounts in sixty or seventy other patients, with intestinal stasis. In the former group, the daily excretion approximately equalled that following ingestion of 0.4 gram of hydroxyphenylethylamine, an amount which might easily produce morbid changes in the vascular system if given daily over a period of many years. The blood-pressure was measured in one patient only, and in this instance was 218 mm. Hg. I intend shortly to work out the relationship between hydroxyphenylacetic acid and diseases of the arteries and liver.

It has been possible to detect certain factors which influence the excretion of the more complex decomposition-products of tryptophane and tyrosin (indoxyl, indolacetic acid, and hydroxyphenylacetic acid). I have described the method of estimating the relative excretion of these substances elsewhere.³ The same convention may be used here as in the measurement of duodenal dilatation, etc., namely:—

(+)	indicates	the presence of	traces
+	"	"	definite amounts
2+	"	"	large amounts
3+	"	"	extreme amounts.

A.—The excretion of tyrosin derivates is proportional to the degree of coliform infection of the ileum, as also is the excretion of tryptophane derivatives.

In 7 cases of extreme coliform infection of the ileum the excretion equalled 1·5 for tryptophane and 1·2 for tyrosin:—

PATIENT	TRYPTOPHANE DERIVATIVES	TYROSIN DERIVATIVES
E. L.	3+	+
L. S.	2+	2+
B. M.	+	2+
F. W.	2+	(+)
E. D.	(+)	+
H. S.	+	+
C. F.	+	+

mean excretion = 1·5 mean excretion = 1·2

In 10 cases of slight coliform infection the excretion equalled 0·7 for tryptophane and 0·7 for tyrosin:—

G. S.	0	2+
D. S.	(+)	+
M. L.	+	(+)
D. M.	+	0
C. J.	+	0
P. G.	(+)	+
A. E.	+	+
R. H.	(+)	+
F. J.	+	(+)
E. T.	+	(+)

mean excretion = 0·7 mean excretion = 0·7

The figures just tabulated uphold the truth of the law. The observation is of importance, in that variations of a symptom found in intestinal stasis have thus been correlated with similar variations in the flora of the small intestine.

B.—The excretion of these decomposition-products is not favoured by a streptococcal infection of the ileum, and is uninfluenced by the presence of B. acidophilus.

In 11 cases in which *B. coli* and streptococci were present in the ileum, the mean excretion of decomposition-products = 1·2. In 10 cases in which coliform bacilli alone were present, the mean excretion = 2·1. In 9 cases in which *B. acidophilus* was present in the ileum, the mean excretion = 1·8. In 8 cases in which *B. acidophilus* was absent, the mean excretion = 1·8.

C.—Excretion varies directly as the degree of ileal stasis.

In 16 cases of marked ileal delay greater than 10 hours, the mean excretion = 2·1. In 7 cases of slight ileal delay (traces of bismuth seen at 8½ hours) the mean excretion = 1·6.

D.—Excretion is uninfluenced by hyperacidity of the stomach.

In 6 cases in which the active hydrochloric acid was between 0·2 per cent and 0·3 per cent, the mean excretion of tyrosin derivatives = 0·9; of tryptophane derivatives = 1·0.

In 9 cases in which the active hydrochloric acid was between 0·1 per cent and 0·2 per cent, the mean excretion of tyrosin derivatives = 0·8; of tryptophane derivatives = 1·0.

This confirms the view that the coliform infection ascends from below and is not due to an inflow of organisms which have escaped destruction in the stomach.

E.—Excretion is increased by hypoacidity of the stomach.

In 7 cases in which the active hydrochloric acid was between 0 per cent and 0.1 per cent, the mean excretion of tyrosin derivatives = 1.2; of tryptophane derivatives = 1.8.

It has already been shown that the coliform infection of the ileum is uninfluenced by the acidity of the gastric contents (see p. 616). The raised excretion of decomposition products in hypochlorhydria must therefore be due to greatly impaired digestion, which results in the arrival of unabsorbed protein hydrolysis products in the lower infected ileum in unusually large amounts.

F.—The excretion is almost abolished by drainage of the ileum, even though the colon is left in situ and ileocolostomy alone performed.

Forty-seven consecutive constipated patients showed a mean excretion of tyrosin and tryptophane decomposition-products = 1.8.

Thirteen consecutive healthy subjects on whom ileocolostomy had been performed two to forty-eight months previously (in 1 case only was colectomy performed) showed a mean excretion = 0.5. In 9 of these cases no traces of indican, indolacetic acid, or hydroxyphenylacetic acid could be found.

At this point it may be mentioned that small amounts of urobilin are commonly excreted by constipated subjects, and that this excretion invariably ceases after ileocolostomy. I cannot suggest any explanation of this phenomenon at present.

To summarize the evidence so far brought forward of ileal putrefaction in constipation: The excretion of bacterial decomposition-products of two different amino-acids, tyrosin and tryptophane, has been shown to vary separately as the degree of ileal stasis and as the degree of ileal infection with coliform organisms.

FIG. 329.—Contraction of a guinea-pig's uterus, caused by β -iminazolyethylamine at a dilution of 1 in 22 millions.

Research along other lines has produced further evidence quite equally convincing. Some strains of coliform organisms are capable of changing histidin into β -iminazolyethylamine (hereafter referred to as β -iminazo). This strain is sometimes called *B. aminophilus*. β -iminazo is a very potent drug, and produces a fall of blood-pressure in man. It displays this power even when taken by the mouth, because it is not destroyed by the liver. It can be estimated by reason of its powerful action on the uterus.⁴ Fig. 329 shows the contraction produced by a solution of β -iminazo of 1-22,000,000 dilution acting on an isolated uterus of a virgin guinea-pig. This contraction was almost maximal, and the uterus shrank to about a third of its original length. Ileal organisms, obtained at operation.

were grown in a 0.1 per cent histidin saline medium, and the amount of β -iminazo produced estimated by comparing the effect of the cultures on an isolated uterus with that of a solution of the drug of known strength. *Fig. 330* shows the effect of such a culture forty-eight hours old and diluted about

FIG. 330.—O. L. Contraction of a guinea-pig's uterus, produced by a forty-eight hours' culture of mixed ileal bacteria in 0.1 per cent histidin saline medium, at a dilution of 1 in 8,000. This corresponds to a conversion of more than 50 per cent of the histidin present into β -iminazo. Blood pressure, 108 mm. Hg; Ileal stasis, marked; Colonic stasis, extreme; Indoxyl, indolacetic, and hydroxyphenylacetic acids excreted in considerable quantities.

8000 times. Careful observations were made on the blood-pressures of the patients whilst lying down and taking an ordinary efficient mixed diet. Fourteen patients were examined, all of whom suffered from chronic constipation of many years' duration, and exhibited colonic stasis in a marked degree. Of these, 6 had a *B. aminophilus* infection of their ileum, with blood-pressures of 108, 106, 104, 102, 102, and 97 mm. Hg respectively; 8 patients had no *B. aminophilus* infection of their ileum. Their blood-pressures were 140, 132,

128, 126, 125, 122, 120, and 114 mm. Hg respectively.³

The correlation of this particular type of ileal infection with the presence of a low blood-pressure, which is the vascular sign of β -iminazo intoxication, proves definitely that at least one symptom sometimes exhibited by constipated patients is determined by abnormal decomposition in the ileum.

Briefly, the coliform infection of the lower ileum in constipation is abnormal because :—

1. It increases with increase in ileal delay.
2. Different strains of coliform bacteria are found in different ileums, *B. aminophilus* being present in a minority of cases.

Some of the symptoms met with in constipation result from bacterial decomposition in the ileum because :—

1. Tyrosin decomposition-products in the urine increase with prolongation of ileal delay, and are almost abolished by drainage of the ileum.
2. Tryptophane decomposition-products in the urine increase with increase in ileal stasis, whilst drainage of the ileum causes them to disappear almost completely.

3. Histidin, acting as precursor of β -iminazolyethylamine, produces a low blood-pressure in those patients only whose ileums contain *B. aminophilus*.

Decomposition in the Colon.—This has received much attention at various times, but is probably quite secondary in importance to ileal decomposition. As stated in the earlier part of this paper, the colon is the site of destruction of residues by an extremely luxuriant bacterial flora. The substances formed are of the simplest nature and, in the amounts absorbed, their pharmacological actions are probably so very slight as to be negligible.

CHRONIC INFECTION THROUGH THE WALLS OF THE INTESTINAL TUBE.

In all likelihood, some of the symptoms experienced in constipation are caused by bacterial toxins generated in the tissues of the alimentary tract, or even in distant tissues infected through this channel. Concerning the pathogenesis of these symptoms, there is little accurate evidence available. It seems probable, however, that the leucopenia, mild anæmia, and relative lymphocytosis, which Dr. White Robertson finds to be a constant feature of chronic intestinal stasis, indicate the working of bacterial toxins which have gained

FIG. 331.—D. W. A CASE OF STILL'S DISEASE. Before colectomy. Note the muscular wasting and the deformity of ankles, knees, wrists, and elbows. Ratio of knee to calf measurement, 1.6.

FIG. 332.—D. W. The same Case as 331, eighteen months after colectomy. Note the disappearance of the deformity around the joints and the increase in muscular and subcutaneous tissue. Ratio of knee to calf measurement, 1.2.

entry through the intestinal mucosa. The great muscular weakness and liability to fatigue from which many of the patients suffer, are reminiscent of the muscular prostration of acute *B. coli* infections, and of the complete asthenia, with advanced changes in the muscle fibres, found in infections with typhoid bacilli, organisms closely related to *B. coli*. Secondary intestinal infections, in which less usual organisms are found in the ileum in addition to those commonly present in intestinal stasis, probably give rise to many symptoms which must be ascribed to the action of bacterial toxins rather

than to food decomposition-products. The most clearly proved instance of such a secondary infection spreading from the ileum to the more distant tissues is the chronic multiple arthritis known as Still's disease.

D. W. (under the care of Sir Arbuthnot Lane), a boy, age 5, had been ill for two years, during the greater part of which he had been treated at one of London's leading hospitals for children. The outstanding clinical features of his disease were marked wasting (his weight was 2 st. 10 lb.) and chronic enlargements of his joints (Figs. 331, 333). He was quite unable to walk, and his pain and weakness were so great

FIG. 333.—D. W. The same Case as 332. Before colectomy. In addition to the features seen in Fig. 331, note the prostration of the patient.

FIG. 334.—D. W. The same Case as 333, eighteen months after colectomy. There is no prostration, and muscular power is equal in degree to that of a healthy boy.

that the assistance of two nurses was required whenever he was moved. The principal joints involved were the ankles, knees, wrists, elbows, and those between cervical vertebræ ; but the changes were not confined to these regions. Swelling was considerable, and chiefly in the peri-articular structures. Most of his superficial lymphatic glands were enlarged. His spleen also was increased in size, and palpable. Blood-counts revealed considerable anæmia of a secondary type. His Wassermann reaction was faintly positive and his von Pirquet reaction negative. He had intermittent attacks of pyrexia (see Fig. 335). Blood cultures made during these attacks gave a pure growth of *Staphylococcus citreus*, and his opsonic index for this organism was 1·8 ; both of which points are of surpassing interest when viewed in the light

of the following history of his alimentary canal. Seven hours were occupied in the evacuation of his stomach, although a little bismuth passed through the pylorus almost as soon as taken. The duodenum was elongated, and bismuth passed through it very slowly. There was great delay in the ileum, and very little bismuth entered the cæcum during the first eight hours. The passage through the colon was sluggish, and after twenty-four hours most of the bismuth was still in the first half of the large intestine (*Fig. 336*, for which I am indebted to Dr. A. C. Jordan).

FIG. 335.—D. W. The same Case as 334. Temperature chart before operation. Showing intermittent attacks of pyrexia.

Dr. Still kindly saw the patient, and agreed that the disease was identical with that peculiar form of chronic multiple arthritis which he personally had described. He expressed the opinion that under the usual recognized medicinal treatment the patient had prospects of life for a few months only. A laparotomy was made which confirmed the x-ray examination. The duodenum was seen to be distended. There was a marked ileal kink, and the pelvic colon was greatly elongated. Ileocolostomy was performed, and cultures made from the ileum. From these a growth of *Staphylococcus citreus* was obtained. It is clear that the stagnant ileum had

become infected with this organism, which had then gained entry to the tissues through the intestinal mucosa and produced chronic arthritic changes in all parts of the body. This circumstance is made even more striking by the fact that cultivations have been made by Dr. Eyre or myself from the ileal contents secured at operations on 55 other patients not the victims of Still's disease, and that in no case has a single colony of *Staphylococcus citreus* appeared. After the operation.

FIG. 336.—D. W. Same Case as 335. The colon twenty-four hours after a bismuth meal.

rapid improvement took place, and in a few weeks' time he was able to play about, entirely free from pain. Nine months later, stiffness reappeared in the vertebral joints, and although there had been no recurrence of pyrexial attacks, he was still thin and anæmic. Cultures were made from the fæces and blood, without detecting the presence of *Staphylococcus citreus*. X-ray examination demonstrated regurgitation into the blinded colon, bismuth being found in all parts of the large intestine as far as the cæcum, forty-eight hours after a bismuth meal. Colectomy was therefore

performed. A year later he was going to school and playing games. He was the backbone of the junior-school cricket eleven.

It is now two and a half years since he was seen by Dr. Still, and his recovery appears to be complete. He has gained 12 lb. in weight during the last fifteen months, and his pallor and weakness have gone. The enlargement of his lymphatic glands and spleen have entirely subsided. His joint movements are almost perfect.

Figs. 331 and 333 taken before colectomy, and Figs. 332 and 334 taken seventeen months after, reveal at a glance the change in the outward contour of his joints, and Fig. 337 shows the healthiness of their x-ray appearance. This case serves as a most striking instance of chronic intestinal infection giving rise to chronic septicæmia, with chronic joint changes, which were cured by eradication of the primary source of infection.

Fig. 338 shows the intestinal condition in F. C., a second patient with Still's disease, who unfortunately has not yet been operated upon.

He is a boy, age 4½ years. He has suffered from increasing pain, stiffness, and swelling in his hands, knees, and spine for fourteen months, during which time he has had four mild feverish attacks. There is slight but general enlargement of his superficial lymphatic glands. His spleen is not palpable. His Wassermann reaction is negative. No blood cultures have been made. The x-ray appearances of his joints are those of Still's disease. His stomach emptied in four and a half hours and his ileum in eight hours, but there is marked delay and deformity in his colon.

Fig. 338 shows the great hypertrophy of the pelvic colon. When seen at the thirtieth hour, bismuth was still present in all parts of his large intestine. Probably this patient also suffered from chronic septicæmia spreading from an intestinal focus.

FIG. 337.—D.W. The same Case as 336. Knee-joint eighteen months after colectomy.

In the concluding paragraphs of this paper, I wish to discuss an almost universal symptom of constipation which probably originates from decomposition in the alimentary tract. It is considered last, because proof that it is not to be classed as an infection through the wall of the canal is still lacking.

Almost every constipated patient suffers from coldness of the extremities, affecting hands, feet, nose, and ears. A slight fall of external temperature is sufficient to cause them acute discomfort in these parts. The phenomenon may be studied by means of a very thin-walled surface-thermometer with a flat bulb. The patient is placed in a room at 19° C. for a short time, and readings are taken of the temperatures of the palm, dorsum, and middle finger-pad of each hand, until these readings are constant. The right hand is then immersed in cold water at 10° C. for a minute, and quickly dried without friction. A further series of temperature readings are taken over a period of half an hour, or until the normal temperature is regained. Tested in this way, the hands and fingers of healthy adults resume their original temperature in five to ten minutes; patients with intestinal stasis require much longer than

thirty minutes. *Figs. 339 and 340* are taken from two healthy individuals of dissimilar habits.

Fig. 339.—M. E., was a woman, age 21, living in London and following a strictly indoors sedentary occupation. Bismuth reached the rectum fifteen hours

FIG. 338.—F. C. A CASE OF STILL'S DISEASE. The colon twenty-four hours after a bismuth meal. Note the great enlargement of the pelvic colon. (This was also the most marked deformity of the alimentary tract seen at the operation on the other boy, D. W. suffering from Still's disease.)

after being taken by the mouth. The urine was free from indican, indolacetic acid, and hydroxyphenylacetic acid. The fingers regained their normal temperature in five minutes.

Fig. 340.—P. M., was a man, age about 45, living in the country and performing a considerable amount of outdoor manual labour. There was no suggestion of

FIG. 339.—M. E. HEALTHY ADULT. Showing normal reaction of fingers after short exposure to cold.

FIG. 340.—P. M. HEALTHY ADULT. Showing normal reaction of fingers after short exposure to cold.

constipation. His urine did not contain indican, indolacetic acid, or hydroxyphenylacetic acid. His fingers regained their normal condition in ten minutes, and his palms and dorsums in a much shorter time.

Fig. 341.—L. C. was a woman, age 32, suffering from severe constipation of many years' standing. She was chosen haphazard from a large number of similar patients. There was marked stasis in the colon of several days' duration. Her urine contained much indican, and a little hydroxyphenylacetic acid. The palm and dorsum of her hand and her finger-tip showed no sign of regaining their normal temperature even after a lapse of thirty minutes.

FIG. 341.—L. C.—PATIENT WITH CHRONIC INTESTINAL STASIS. Showing greatly delayed reaction of fingers after short exposure to cold.

The phenomenon is very definite indeed, and is abolished by drainage of the ileum; but the explanation is still lacking. It may be that small but persistent doses of pressor amines, which are quite inadequate to affect the blood-pressure, are yet sufficient to constrict the peripheral arterioles if aided by a cold stimulus, and produce thereby prolonged coldness of the extremities. It may also be related in some way to Raynaud's disease, which, studied from the point of view of chronic intestinal infection, affords many points of interest.

G. W. (under the care of Sir Arbuthnot Lane), a man, age 24, had suffered from Raynaud's disease for nine years.

HISTORY.—His symptoms commenced with attacks of coldness of the fingers and toes during the winter. In later years the attacks involved his hands and feet, and even spread as far as his elbows and knees. At first they came on during the winter months only, but lately they had frequently occurred in the summer also. During the attacks, the affected parts usually became white and 'dead,' being devoid of all sensation; sometimes, however, they were blue and cyanosed. As early as eight years ago, trophic ulcers appeared on the finger-tips, and these

recurred, with much destruction of the superficial tissues in succeeding years. For three years he had suffered also from syncopal attacks, which showed no relation to the weather or to the peripheral spasm in his limb vessels. They varied in frequency from one per month to three or four per week. At these times he lost consciousness completely, and on waking up again felt drowsy for several hours and experienced severe headache, with palpitation and throbbing in his neck. He did not usually recover in time to see his friends raising him from the ground where he had fallen. These attacks were not associated with incontinence of urine or biting of the tongue. No history was obtainable of dyspnœa on walking, of precordial pain, or of œdema of the legs.

His alimentary history was as follows: In his youth, defæcation had been regular, and unaided by artificial means; but during the last few years he had suffered from alternating attacks of constipation and diarrhœa. In his diarrhœal condition his motions were watery, but normal in colour and free from blood and mucus. Sometimes his bowels were open sixteen times in twenty-four hours, but there was no coincident abdominal pain. Before the onset of diarrhœa his appetite

FIG. 342.—G. W. A CASE OF RAYNAUD'S DISEASE. Note the symmetrical and severe scarring of the finger-tips.

became poor, but he rarely suffered from indigestion pains of any kind, and was never troubled by heartburn, nausea, retching, vomiting, or gastric flatulence. No other symptoms could be elicited. During the last two years he had received almost continuous medicinal treatment, including faradism and light baths, but no improvement had taken place. The last few months he had spent in an infirmary, being so crippled that he could no longer earn his living.

ON EXAMINATION.—He was seen to be a thin man of normal height, with cold, bluish extremities. He walked very slowly and with a limp, because of the stiffness of the joints and tissues of his feet. His hands were clawed, and so stiff that he had great difficulty in dressing himself. The fingers were covered with scars, which reached their maximum distribution near the tips of the fourth and fifth digits. The terminal segments of the little fingers were mere cicatrices supported by bone (*Fig. 342*). The severity of the scarring diminished towards the radial margin and towards the hand and forearm, but four small scars marking the site of trophic ulcers were present about the wrist and lower part of the left forearm. Similar symmetrical

changes were found in his feet. Here scarring was most marked on the big toes. On the inner aspect of the left leg, a little above the ankle, was a scar of a large and recently healed ulcer. It is interesting to note that the bones also showed changes. *Fig. 343* illustrates great rarefaction of the phalanges of the hand, which corresponds accurately in its distribution with that of the changes in the superficial structures. Evidently the arteries to the bones partook in the spasm at the same time as those supplying the soft tissues of the fingers. There were no scars on the ears or nose. The physical signs in the alimentary system were hardness, tenderness, and immobility of the terminal coil of the ileum, slight tenderness over the third part of the duodenum, with hardness of the pylorus and slight tenderness over the iliac

FIG. 343.—G.W. The same Case as 342. Note the bony atrophy, corresponding in distribution to the scarring on the left hand (see *Fig. 342*).

Appendix.—Bismuth entered its lumen. It was freely movable, not tender, and not controlling the ileum.

Colon.—The cæcum was in the right iliac fossa. The transverse colon was elongated, and dipped into the pelvis even in the horizontal position. There was some elongation of the pelvic colon, and distention of the rectum (*Fig. 345*). The iliac colon was tender, and bound down. Bismuth entered the cæcum in two and a half hours, and reached the rectum in twenty-six hours; but much remained in the transverse, descending, and pelvic colons until the forty-fifth hour, although the bowels were opened at the twenty-fourth hour.

In this way were demonstrated dropping of the stomach, elongation of the duodenum, transverse and pelvic colon, and kinking of the ileum. There was marked stasis in the stomach, duodenum, and colon, and a little in the ileum.

A routine examination was made of his lungs, nervous system, joints, thyroid gland, heart, and blood-vessels; but no further abnormality was detected beyond a faint hæmic bruit.

colon. His appendix was not felt. No sign of sepsis could be found in his mouth, nose, or pharynx.

X-ray-and-bismuth examination furnished the following results:—

Stomach.—The greater curvature dropped to the pelvic brim in the vertical position. About eight hours were required for its evacuation.

Duodenum.—The first and second parts filled readily, but bismuth entered the jejunum very slowly. The duodenum was elongated, the vertical part being $4\frac{1}{2}$ in. long. It was also dilated, and showed strong writhing movements, with regurgitation of its contents (*Fig. 344*). The tenderness of the third part was confirmed.

Ileum.—There was only slight delay in the ileum, but the last coil was fixed at a point about 1 in. from its termination, where it became kinked in the vertical position after the entry of the bismuth into the cæcum.

The tenderness of this coil was confirmed during the screen examination.

His blood yielded the following data :—

Brachial blood-pressure, 115 mm. Hg	
Red-count, 5,040,000 cells per c.mm.	
Hæmoglobin, 78 per cent	
Colon index, 0.8	
White-counts, (at 10 a.m.) 13,400, (at 6 p.m.) 12,200: mean, 12,800.	
Differential-count, Polymorphonuclears	48 per cent
Lymphocytes	50 "
Eosinophils	2 "
Hyalines	4 "
Mast-cells	1 "

He thus displayed anæmia of a secondary type, and a positive lymphocytosis. His urine gave distinct evidence of a coliform infection of the ileum. A twenty-four hours' specimen was amber-coloured, and its specific gravity 1017. Sugar, albumin, urobilin, acetone, diacetic and indolacetic acids were absent, but a little indican and considerable hydroxyphenylacetic acid were present.

Adrenalin 1-1000 did not produce any dilatation of the pupils when instilled into the conjunctival sac.

OPERATION.—Laparotomy was performed by Sir Arbuthnot Lane, and the x-ray findings accurately confirmed. The colon was removed, and the ileum joined to the pelvic colon. Contents were withdrawn from the duodenum for bacteriological examination. At the commencement of the operation, the last coil of ileum was isolated from the colon by ligature, and its contents were examined about an hour later.

EXAMINATION OF INTESTINAL CONTENTS.—*Duodenal Contents.*—The fluid was of a pale straw-colour, faintly opalescent, and strongly alkaline to litmus. Plate cultures from five loop-fuls on nutrose agar gave two colonies of *Streptococcus brevis*. One c.c. of the fluid was inoculated into 500 c.c. of peptone broth and incubated for one week. The formation of pressor bases, including ergotoxin, was disproved by rendering the broth alkaline with sodium carbonate and extracting it with ether. The ether was washed, and allowed to evaporate at room temperature. The residue taken up in saline was injected into a 'spinal' cat without producing any effect on its blood-pressure.* The conclusions to be drawn are that no pathogenic organisms other than a few short-chained streptococci were present in the duodenum.

Ileal Contents.—The chyme was brown, gelatinous, odourless, and markedly alkaline to litmus. Plate cultivations yielded 200 colonies of coliform organisms,

FIG. 344.—G. W. The same Case as 343. Showing dilatation and elongation of the duodenum. P, Pylorus. D1, 2, and 3, Duodenum, parts 1, 2, and 3 respectively.

* This injection under the Act 39 and 40 Vict. c. 77, was performed by Dr. P. P. Laidlaw,

23 colonies of a short-chained Gram-positive streptococcus which produced a mauve pigment and liquefied gelatin, and 30 pale colourless colonies of Gram-positive streptobacilli. The last-mentioned organism was in the form of long narrow rods, and grew freely in blood agar and blood-serum in small pin-point colonies. It formed acid from galactose, traces of acid from maltose, laevulose, and dextrin, but none from dextrose, lactose, dulcitol, and glycerin. It did not alter litmus milk, and grew very slowly on gelatin without liquefaction. A few minute colonies also appeared on

FIG. 345.—G. W. The same Case as 344. The colon twenty-seven hours after the administration of bismuth. Note the elongation and ptosis of the transverse colon, and the great elongation of the pelvic colon. (Patient in supine position.)

agar. It resembled the predominant organism seen on direct examination of the ileal chyme. It will be seen that it grows well on blood media only, and rarely forms acid in sugar media. Spores were not observed in any of the cultures, and there was no gas formation.

I do not claim that these organisms are the cause of Raynaud's disease, but their presence in the ileum is at least suggestive. Many other cases are needed before definite conclusions can be drawn.

Ileal contents were also inoculated into 500 c.c. of peptone broth, and organic bases extracted as before. The extract caused a distinct rise in blood-pressure in a 'spinal' cat, showing the formation of pressor bases. It did not cause any reversal of the adrenalin effect, from which observation it must be concluded that ergotoxin was absent (*Fig. 346*).

The formation of the pressor body by the ileal flora is of interest in connection with the suggestion that the coldness of the hands of constipated patients is due to a reaction of the peripheral arterioles to the combined stimulus of slight cold and small doses of vasoconstrictors. The patient's hands became warm immediately after the operation, and have remained warm persistently for seven weeks. Although before drainage of the ileum, ordinary cold water induced syncopal attacks in his hands, he could now, seven weeks after operation, wash in a mixture of ice and water in a moderately cold room with impunity. The reaction of his hands to cold water at 10° in a room at 19° C. is shown in *Fig. 347*, and contrasted with the much slower reaction of an ordinary constipated subject (*Fig. 348*). It will be seen to compare favourably with the reactions of the healthy adults already referred to (see *Figs. 339 and 340*). When his finger-tips were tested, the reaction was similar to that of simple constipation, but the tissues in the locality had been extensively destroyed and were largely cicatricial, so that the comparison was not a fair one.

One of the most striking features of his recovery was the speed with which the stiffness left his hands and feet. His hands became quite supple, and the clawing disappeared within twenty-four hours: seven weeks later he was walking about freely without a limp.

Although to a critical mind the suggestion that this case of Raynaud's disease was due to an infection of the alimentary tract may not seem to have been completely proved, yet the following facts are significant:—

1. Two unusual organisms were present in the ileum in great numbers.
2. There was marked chronic intestinal stasis.
3. The ileal flora produced pressor bases from peptone.
4. The disease was cured by colectomy.

FIG. 346.—G. W. The same Case as 345. Blood pressure tracing from a 'spinal' cat, showing the effect of pressor bases produced from peptone by the mixed ileal bacteria. Note also that the injection did not produce any reversal of the adrenalin response.

FIG. 347.—G.W. The same Case as 346. Seven weeks after colectomy. The curve shows that the reaction of his hands after a short exposure to cold was almost normal. (Contrast this curve with Fig. 348.)

FIG. 348.—L. C. CHRONIC INTESTINAL STASIS. Note the great delay in the reaction of the hand to the cold stimulus, and contrast it with the rapid response shown in Fig. 347.

CONCLUSIONS.

The main facts which have been substantiated in this paper may be briefly summarized thus :—

1. Dilatation of the duodenum is usually associated with gastric stasis.
2. Dilatation of the duodenum varies directly as the degree of ileal stasis, and—apart from this—shows no relationship to the ileal kink.
3. Epigastric tenderness in constipated subjects is usually experienced over the third part of the duodenum; not over the pylorus.
4. Typical 'hunger' pain may arise when food in the lower ileum produces duodenojejunal obstruction.
5. A pure culture of a long-chained Gram-positive hæmolysin-producing streptococcus was obtained from the duodenum of a man with severe anæmia and pigmentation.
6. The richness of the living bacterial flora of the colon is immeasurably greater than that of the last coil of the ileum.
7. The degree of ileal infection with coliform organisms is proportional to the degree of ileal stasis.
8. A marked ileal kink acts as a protective barrier against invasion of the ileum by coliform organisms.
9. The infection of the ileum with coliform organisms, and the dilatation of the duodenum, vary in a parallel manner.
10. The infection of the ileum with coliform organisms is uninfluenced by the acidity of the gastric secretion.
11. Urine of constipated patients often contains urobilin.
12. Urine from constipated patients often contains hydroxyphenylacetic acid.
13. The excretion of the more complex tyrosin decomposition-products varies directly as the degree of ileal infection with coliform organisms.
14. The excretion of tryptophane decomposition-products varies directly as the degree of ileal infection with coliform organisms.
15. The excretion of indoxyl, indolacetic acid, and hydroxyphenylacetic acid is uninfluenced by an infection of the ileum with streptococci or with the *B. acidophilus* of Moro.
16. The excretion of the last-mentioned substances varies in proportion to the degree of ileal stasis.
17. The excretion of tyrosin derivatives is uninfluenced by hyperchlorhydria, but increased by hypochlorhydria.
18. The excretion of tryptophane derivatives shows the same relationship to gastric secretion as does that of the tyrosin derivatives.
19. The excretion of indoxyl, indolacetic acid, hydroxyphenylacetic acid, and urobilin is almost entirely abolished by ileocolostomy.
20. An infection of the ileum with *B. aminophilus* occurs in constipated patients with a subnormal blood-pressure, but not in other constipated patients.
21. Chronic infection of the ileum with *Staphylococcus citreus* has been shown to be present with chronic septicæmia due to the same organism, and with the chronic joint, lymphatic, and splenic changes classified as Still's disease. The constitutional changes, and those in the joints, lymphatic glands,

and spleen were abolished by colectomy. Fifty-five ileums of patients without Still's disease were free from *Staphylococcus citreus*.

22. The hands of constipated patients recover from exposure to cold at a very much slower rate than do the hands of healthy subjects.

23. A patient with Raynaud's disease was found to be the subject of chronic intestinal stasis. In his ileum were large numbers of an unusual Gram-positive bacillus and a short streptococcus. Colectomy restored his hands to a normal condition, in which they showed normal reaction after exposure to cold. His ileal flora formed pressor bases from peptone.

The presence of alimentary deformities referred to in this paper was in two instances confirmed at operation by Mr. C. H. Fagge, and in all other instances by Sir Arbuthnot Lane, unless a statement appears to the contrary.

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RADIOLOGICAL STUDIES OF THE LARGE INTESTINE.

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To write a paper on the x-ray examination of the large intestine would have been comparatively simple a few years ago. One would have been content to take the anatomical structure and deal with it according to the circumscribed views that we inherited. To-day it is different; for we know that the large intestine is but one part of a complex organization, so closely linked together that it is almost impossible to separate out the constituent anatomical parts and deal with them separately. As more and more evidence accumulates to show the interdependence of the whole alimentary tract, the conception of 'watertight' compartments with anatomical boundaries, in the alimentary canal, is disappearing. Here and there we get glimpses of reflex spasms—as, for example, a pyloric spasm from some apparently slight abnormality in the ileocecal region—that indicate a network of nerve centres, relays, and sub-centres that are as yet beyond our ken.

The physics of osmosis, a long line of test-tube experiments with secretions and ferments, a vague and quite unessential idea of some movement of the stomach and intestine, used to fill the whole field of our conceptions of digestion. Perforce we had to be content with it. In recent years it has become possible to study the mechanics of digestion, and the movements of the food through the tract, and it has become more and more evident that the conditions with which the surgeon is called upon to deal are those that are associated with faulty *mechanism* rather than faulty *digestion*; with the result that there is perhaps a tendency to forget that there is a chemistry, as well as a mechanism, of digestion. It is the mechanical factor of digestion that is to-day passing under review; the *fons et origo* of irregular muscular