THE MICROCHEMICAL CHANGES OCCURRING IN APPENDICITIS, WITH A NOTE ON THE INCIDENCE OF THE DISEASE IN VARIOUS COUNTRIES

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In observations previously recorded¹ I have shown that intestinal sand and appendix concretions are allied in chemical constitution, and also that abnormal bodies sometimes found in the intestine and producing symptoms of disease are formed of compounds of saturated fatty acids.

These observations led to the conclusions that there are conditions in the intestines in which certain soaps or other insoluble compounds of fatty acids are not absorbed by the intestinal mucous membrane, and that with the presence of these conditions certain diseases of the alimentary tract are related. The fats and soaps found in these conditions were compounds of saturated fatty acids. The richness of these bodies in calcium and fatty acids which are constituents of the excretion of intestinal mucous membrane point to their originating in the intestine as a result of some excess in excretion or defect in absorption.

Recently I have had opportunities of observing further cases in which appendicitis has been associated with mucous colitis or with intestinal lithiasis. In one case of appendicitis with abscess, both before and after operation intestinal sand was found in the faeces in large quantity. In another case, a female who had been operated upon for appendicitis, there was present marked mucous colitis, and intestinal sand was found in fair quantity.

This contribution records further observations on the relation of abnormal fat processes to the aetiology of appendicitis, and shows that similar changes occur in the wall of the appendix itself.

1. 'Abnormal Fat Assimilation,' etc., *Bio-Chemical Journal*, Vol. II, p. 395, 1907

As far back as 1813 Weigeler¹ examined several stones removed from the appendix of a boy eighteen, who died with all the symptoms of appendicitis. He regarded the stones as biliary calculi which had undergone change from the action of intestinal secretions, and he subjected them to chemical analysis, the results of which were as follows :—

Lapidis granum 1 constabat e.					
Materia pingua adiposa	...	...	...	...	0.60 gramme
Phosphat calcis	...	...	...	...	0.30 „
Materia animali...	...	...	...	...	0.08 „
Ponderis diminutio erat	...	...	...	...	0.02 „
					<hr/>
					1.00 gramme

Rokitansky in 1855 considered catarrhal inflammation of the appendix to be due to faecal concretions, and he believed that this inflammation might persist as a chronic morbid condition. Since then the fleeting references to these concretions are unfortunately the result of only cursory examination, as is shown by their being called faecal concretions, or even the stones of various fruits.

I have had the opportunity of examining a large number of concretions, and not one have I had the slightest difficulty in cutting and of seeing that they are all concentrically laminated, and, therefore, formed in the appendix itself.

Vallee and Bryant² state that they have found faeces in 70 per cent. of appendices examined.

I have examined the appendices of 100 consecutive post-mortems in adults, and in only three was true faecal material present ; in the remainder there was a dark slimy mucoid material, in some cases not unlike faeces in consistence, but not showing the same pigmentation as true faeces.

Expressing this material into alcohol I have been able to isolate a small amount of fat from it, and this gave a low iodine value (the quantity examined was too small to give an accurate figure). The nature of the fat thus resembles the fat isolated from the loop of intestine in the case quoted in the previous paper.

1. Quoted from Kelly's *Vermiform Appendix and its Diseases*.

2. *Ibid.*, p. 148.

I was fortunate enough in one case to find in the appendix small granules looking exactly like intestinal sand, showing the likeness not only in nature but also in the formation of this substance and the appendix concretion.

The frequency of these concretions is undoubted. Deaver¹ gives the following figures :—

Variety	Percentage of class of case	Percentage of presence of calculus
Acute Catarrhal	3·7	None
Acute Interstitial	15·9	6·2
Acute Ulceration	59·4	22·3
Acute Gangrenous	20·9	10·2
Chronic Catarrhal	1·5	Rare
Chronic Obliteration	1·5	None
Chronic Interstitial	0·97	1·55

The great frequency of occurrence points to some close relationship to the disease, and as previous writers have considered them from the standpoint of their being inspissated faeces, it will be of advantage to consider their formation in the light of their constitution as revealed by the following observations.

I have shown² that they are undoubtedly formed in the appendix, and Kelly states :³ ‘The histological examination shows that the most important factor in the formation of the calculus is the mucus secreted by the glands of the mucous membrane. The mucus, which is deposited in layers round the central nucleus, becomes desiccated, and the lime salts are deposited secondarily. Frequently fragments of epithelium, a few leucocytes, and altered blood are found in the different layers. Ribbert noted that in favourable specimens stained with Weigert’s fibrin stain, the outer layers of mucus may be seen to be directly continuous with the glands of Lieberkühn. In one case, besides the two large enteroliths in the canal of the appendix, *I found three smaller bodies embedded in the mucous membrane, which had evidently developed within gland lumina.*’

This latter statement is full of meaning in view of my findings, to be described later.

1. Battle and Corner, ‘*The Surgery of Diseases of the Appendix.*’

2. ‘Abnormal Fat Assimilation,’ *Brit. Med. Journ.*, July 27, 1907.

3. *Loc. cit.*, p. 300.

Kelly gives further evidence of this mode of formation of the calculus.¹

Concretions do not occur in all cases of appendicitis, but the following investigations into the nature of the changes taking place in the appendix show that the process by which they are formed may go on in the wall of the appendix and give rise to morbid conditions which allow of easy invasion by micro-organisms, and thus to the acute and chronic forms of appendicitis. These changes are the formation of calcium soaps in the submucosa and mucosa of the appendix. These soaps, normally expelled into the lumen of the appendix and then into the caecum, in cases of appendicitis block up the lumen of the glands or (as in many of the specimens obtained) form a ring in the submucosa.

The micro-chemical tests which I have employed are the same as those used by Klotz² and Lorrain Smith.³

These methods depend upon the following chemical facts :—

Osmic acid stains neutral fats black ; it does not blacken palmitic and stearic acids.

Sudan III, scharlach R, and other similar bodies stain neutral fats a bright pink, whereas they stain soaps a pinkish yellow. The difference in these two colours is easily seen in the specimens obtained.

Nile-blue sulphate stains neutral fats pink, and stains fatty acids violet.

Silver nitrate forms an impregnation of silver oxide on calcium compounds.

Petroleum ether dissolves neutral fats from a specimen, but not soaps. This can be used as a further test for differentiating these two compounds.

1. *Loc. cit.*, p. 301.

2. *Journal of Experimental Medicine*, Vol. II, No. 6, Nov. 25, 1905.

3. *Journal of Pathology*, p. 283, 1907.

THE MICRO-CHEMICAL CHANGES IN THE WALL OF THE APPENDIX

Sections of appendices stained by the above methods show the colour reactions from which the nature of the chemical changes in the wall have been deduced. The specimens were obtained from appendices removed by operation and placed immediately in formol.

Post-mortem specimens have been examined, but as the primary effect of autolysis is fatty degeneration, the true condition of the cells in life is not to be obtained from such specimens.

Zuckerkindl¹ has shown that, as the result of age, the mucous membrane undergoes atrophy, and the glandular structures desquamate. At the same time, or occasionally before this time, the submucous coat undergoes thickening, and *fat* accumulates at this part of the wall.

A normal appendix from a child, obtained at operation, is required as a standard. This I have not been able to obtain, and failing this, I have compared my sections with those of an appendix (apparently healthy) of an adult, removed from a hernial sac. This abnormal position would possibly interfere with its function to some extent, but nevertheless the specimen shows little fatty degeneration of the mucous membrane, and only traces of soaps in the submucosa. These slight changes may be considered to be due to either normal involution changes or to the abnormal position of the appendix.

Stained to show the calcium present, there is some to be seen in the mucous membrane at certain points. Sections from diseased appendices treated by the same methods and under the same conditions show most striking differences: differences which are so great as to be immediately obvious in sections stained in bulk and observed macroscopically. The changes cannot be due to involution changes, as they are seen in specimens obtained from cases occurring in children.

These sections show a *large increase in the production of calcium soaps*, both in the mucous membrane and in the submucosa. In some of the specimens almost a complete ring of soaps is to be found in the submucosa.

1. Nothnagel, *Diseases of the Intestines and Peritoneum*, 1905, p. 382.

A change in the submucosa has been frequently recorded as a marked thickening. This thickening is in the above specimens seen to be due to the laying down of these soaps. Small quantities of fatty acids are also found in the submucosa by the Nile-blue sulphate method.

Staining by silver nitrate shows the presence of calcium in definite quantity in the submucosa of the diseased appendices.

These observations, therefore, show that in appendicitis there is a marked change in the wall of the tube—a change characterised by the increased production of calcium soaps in the mucous membrane, and more particularly their formation in the submucosa.

A few of the specimens show the secretion or rather excretion of these soaps into the lumen, and thus confirm Ribbert's observation that it is the mucus, as he called it, which is poured forth which forms the concretion. This is further proved by the fact that the chemical constitution of the excretion and concretion is the same.

That this process can, in rare instances, go still further is shown in a case recently published.¹ A man aged forty-one had his appendix removed for an acute attack of appendicitis. The appendix was unusual in shape, and opened into the caecum by a very wide orifice. Distal to this orifice was a marked hypertrophy of the muscular layers. This extended for about half the length of the tube. Beyond was a dilated portion full of white pultaceous material. Some of the material was examined qualitatively and shown to contain calcium soaps and calcium carbonate, the latter apparently in fair quantity. The calcium carbonate was formed as the result of further degeneration of the calcium soaps.

The orifice of this appendix was so abnormally wide that it is inconceivable that the material could arise from the intestine, as there was such free drainage, and the offending material had accumulated behind the hypertrophied muscle.

These observations show that in appendicitis there is a change in the nature of the fatty compounds far in excess of any I have so far been able to observe as the result of involution changes.

1. *Brit. Med. Journ.*

The important question consequently arises whether this change is the cause of the disease, or whether there is some underlying cause which produces these changes and the disease. From what we know of the formation of these calcium soaps, it is a very slow process, and, therefore, must have commenced long before the attack of acute disease. It may, therefore, be presumed that these fat changes go on, produce the altered condition of the mucous membrane, or in some instances form an impermeable barrier in the submucosa, cutting off the nutritive supply to the already altered mucous membrane. The invasion by organisms is then rendered much easier.

The nature of the fats in the food determines to some extent the nature of fats in the tissues. It would, therefore, seem that as these abnormal processes are set up by saturated fatty compounds (palmitic and stearic) and not by unsaturated fatty compounds (oleic), the nature of the fat in the diet might have some influence in their production. This is made still more likely when we recognise that the absorbability of these two forms of fat is so different.¹

INCIDENCE OF APPENDICITIS

I have, therefore, endeavoured to find if the nature of the food fats has any relation to these pathological processes—whether an excess of saturated fat (as in beef and mutton) in the diet is more liable to produce the disease than unsaturated fat (as in olive oil, etc.). I wrote to His Majesty's representative in all countries having a population of over two millions, and from a large mass of correspondence I quote the following which have relation to the subject.

For comparison it may be stated that the death-rate in England from appendicitis in 1902 was 90 per million persons living.

SPAIN.—Dr. Glendinning writes : ' The facts are, firstly, that it is comparatively rare. In my occasional visits to various hospitals during the year I have not seen a single case of appendicitis. Secondly, it is slightly more common among the aristocratic classes. Dr. Guttierrez, who has the largest consulting practice in Madrid, informs

1. *Brit. Med. Journ.*, July 27, 1907.

me that he has personally seen four cases in the last year, and has heard of another three as being seen by colleagues.'

Examining the statistics, I find that the death-rate from 'appendicitis and inflammations of the iliac cavity' is twenty per million.

Dr. Glendinning states that there is not as much oil in the diet of the Spanish people as is commonly supposed.

ITALY.—An Italian doctor visiting the Royal Infirmary, Liverpool, stated that the disease was comparatively rare in Italy, but Professor Bastianelli writes that the disease is common in Rome and that part of the country. The statistics of operations which Professor Bastianelli sends me show that an average of 156 cases are operated on in Rome annually from a population of 500,000.

This would give the incidence as far less than that of Liverpool.

SWEDEN.—The death-rate is about 16 per million. The consumption of meat is about 59 lbs. per head per annum, or about $2\frac{1}{2}$ oz. per diem, which is less considerably than in the English diet.

DENMARK.—The death-rate is about 12 per million. 'It may be said, however, that the staple diet will be about the same as that of Great Britain, only that less meat and vegetables are eaten, whereas more potatoes, rice, and other starch-containing articles are consumed.'

CAIRO.—Out of 13,671 cases admitted to the Kaisr-el-Ainy Hospital there were *only fourteen* cases of appendicitis. This is an extremely low percentage compared with English hospitals.

The registrar states that beans cooked in oil is a very common dish among the natives.

ICELAND.—The chief physician writes: 'The disease is in my own and other medical officers' opinion of the same comparative occurrence here as in other countries. Fats are consumed in a higher degree than among common people in most other countries.'

Unfortunately the nature of the fats is not stated, but it is safe to assume that meat fats are meant.

BELGIUM.—Fat is taken in large quantity, particularly in the form of butter (which contains a good deal of *unsaturated* fat—of *oleic* acid), lard, and margarine.

Dr. Nicoleb writes ‘that it is his own impression that appendicitis is not a frequent disease.’

GREECE.—Out of 28,067 cases admitted to hospitals, there were only 393 cases of appendicitis (a figure far less than that given for the Liverpool hospitals).

‘A good deal of the cooking is done with olive oil and butter.’

NORWAY.—‘The disease is very frequent in this country. It seems to be more so in the greater towns than in the rural districts.’

‘With more prosperous circumstances and a more liberal diet the frequency seems to increase.’

‘Safe statistical statements as to the diet do not exist.’

CHINA.—‘Appendicitis is an extremely rare disease in China.’

‘Some time ago inquiries made through the *China Medical Journal* among all the medical practitioners show that forty-four had rarely seen the disease, sixty-nine had seen a few cases but thought the disease uncommon, forty-nine had not seen any cases at all.’

‘In the Public Mortuary, out of 2,140 post-mortems, appendicitis is not once mentioned, nor does it occur in the list of 215 surgical operations performed in the Government Civil Hospital.’

‘Foreigners resident in China have no immunity from the disease.’

Diseases of the alimentary system are *more common* than those of all the other systems.

‘The system of diet, bolting of food, etc., are the main causes of the frequency of digestive troubles.’

‘It will thus be seen that there are two outstanding points of difference between the Chinese and European dietaries, viz., *the lessened quantities of sugar and meat in the former scale.*’

‘Meat is eaten fresh, and *there is an entire absence* of tinned and frozen meats, which by their cheapness and adequate supply have increased the consumption of meat per head during the past decade or two in Europe—especially in England.’

‘No one here has been able to offer, as yet, any feasible explanation of the freedom from appendicitis, though most doctors think *there must be a predisposing cause in the European diet.*’

INDIA.—I have no statistics personally, but quote from the *Lancet*, April 18, 1908, p. 1,162: ‘It seems to be clear that appendicitis is *rare* in India.’

Mr. James Harris, L. M. and S., the writer of the article in Madras, suggests the simple diet of the people as the cause of their comparative immunity. He further suggests the frequent habit of purgation and the mode of defaecation as factors.

Lewkowitsch¹ states that linseed and rape oils (markedly unsaturated) are largely taken in India.

ABYSSINIA.—The Medical Officer of the British Legation states: ‘During a residence of eight years or so in this country, and a practice among all classes of the population, I have never come across a single case of appendicitis, nor have my colleagues ever met with what could be called an authentic case of the above malady. . . . A considerable amount of melted butter is the principal fatty constituent of their diet.’

HOLLAND.—Statistics obtained from Dr. C. Eykman show that the incidence in this country is about the same as in England—from 88 to 113 per million. It is more frequent among males. He states that ‘as everywhere else the diet of the well-to-do classes differs from the poorer classes in that the former consume a greater quantity of meat, and in that connection of albumen and fat.’

ENGLAND AND AMERICA.—There seem to be two definite facts about the disease in these countries: first, that it is more frequently a disease of the rich than of the poor; and second, that it is on the increase.

There is no doubt that in these countries meat is eaten in large quantity, and that the facilities for obtaining meat are much better now than a few decades ago, when the disease was much less common.

The above statistics would tend to show that the incidence of

1. *Chemical Technology of Oils and Fats*, Vol. II, 1904.

the disease is greater in those countries where much saturated fat is consumed.

As the statistics of this disease are as yet in all countries incomplete, it is difficult to draw deductions from them, but they are worthy of consideration.

CONCLUSIONS

From clinical evidence and pathological and chemical observations it would appear that there is produced in the course of the changes in the intestinal wall an abnormal condition associated with formation of calcium soaps. These calcium soaps when formed in the intestine in excess produce intestinal sand, and associated with this there are symptoms of colic with, under some circumstances, an associated form of mucous colitis, or, as the French authors call it, muco-membranous enterocolitis.

This change taking place under similar conditions and probably from the same causes in the appendix, where there are poorer opportunities for the discharge of the deleterious bodies, is probably an important factor in the aetiology of appendicitis.

The cause of these pathological changes is possibly an excess of saturated fats in the food-stuffs, giving rise to the formation of calcium soaps of more saturated fatty acid in the mucosa and submucosa than is normally the case. These soaps are not so easily absorbed as the soaps of the unsaturated fatty acids, and, therefore, act as foreign bodies in the wall, and at times in the lumen as a concretion.

My thanks are due to Sir James Barr for valuable aid in the collection of statistics, the physicians and surgeons of the Royal and Children's Infirmarys for many specimens, and to Professor Benjamin Moore for his constant advice during the conduction of these researches.