

THESIS ON SPRUE.

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INTRODUCTION.

Sprue has been described by Sir Patrick Manson as the most serious, chronic disease affecting Europeans in the Tropics. It is not an extremely common disease, as common for example as dysentery, but its prevalence is increasing and it has become quite a serious menace to Europeans whose work necessitates their residence in the Tropics. It is not essentially a disease peculiar to Europeans in the Tropics, although they seem to be more liable to it than natives. Manson Bahr has recognised cases among natives in Ceylon and Ashford has recognised cases among natives in Porto Rico. Manson who worked in China never recognised a case in pure Chinese. In the writer's work in Hong Kong he has not yet observed a case among the Chinese.

A good deal of work on Sprue has been done in the last few years. The writer thinks that the work, which has influenced treatment by medical men in the tropics most, is that of H.H. Scott. Scott was Government Bacteriologist in Hong Kong for some years and himself developed Sprue, which makes his work all the more interesting. After trying all the then known remedies, he was eventually cured by calcium and parathyroid extract, which forms the basis/

basis of his treatment. This treatment is now fairly generally used by practitioners in the Tropics.

Sprue has been recognised by writers on Tropical Medicine for many years. It has been called "tropical diarrhoea," "diarrhoea alba," "apthae tropica", "Ceylon or Singapore sore mouth", "psilosis linguae" and "athrepsei coloneale athropique."

By the term "sprue" is understood a form of chronic catarrhal inflammation of the whole or part of the mucous membrane of the alimentary canal, generally associated with disturbance of the functions of the liver and pancreas. This manifests itself by the passage of large, pale coloured, pultaceous, frothy stools, progressive emaciation and finally by marked anaemia of the pernicious type. The disease is rarely acute. More generally it occurs in a chronic form and it may exhibit periods of latency extending over a number of years. It may occur as a primary disease or it may supervene on other affections of the bowels. It is very slow in progress and unless properly treated tends to terminate in atrophy of the intestinal mucosa. When this occurs, it is doubtful if there is any treatment of avail and the patient dies a slow, lingering death. There is hardly any other disease in which release from suffering is so gradual.

The utmost importance is now laid on the early diagnosis of the condition, as it is then most amenable to/

to treatment; but in the earliest stages of the disease, none of the classical symptoms may be present. This has been the difficulty in the past. This has been the cause of the sad procession of clinical failures drifting home, most of them to die within a few months of their return. It is with the practitioners in the tropics that the responsibility rests. The disease must be recognised and treated there, at the earliest opportunity. Some writers say that the patient must leave the tropics. The majority of people are unable to do that. It means giving up their work, and ruin for themselves and their families. This however may not be necessary if the disease is attacked at its commencement.

Sprue has been compared to the coeliac disease of childhood. Apart from the fact that the motions in both are pale coloured and contain an excess of fat, there is no resemblance. Coeliac disease always originates in childhood and, even without treatment, may disappear as maturity is reached. The essential feature is disordered fat absorption and it has nothing to do with intestinal disease. In many cases there is no diarrhoea and usually no ulceration of the tongue.

On the other hand the comparison of Sprue and Pernicious Anaemia shows many points common to the two diseases. The anaemia in late cases of sprue is of/

of the pernicious type with high colour index of the blood. Pernicious anaemia also shows the following symptoms which are commonly found in late cases of sprue, viz: yellowish pallor, sore mouth, vomiting, dyspepsia, diarrhoea, free HCl absent from gastric contents, numbness and tingling, remissions, low blood pressure and petechial haemorrhages.

The anaemia of late sprue is an interesting point, because a similar type of aplastic pernicious anaemia is produced by the presence of the ^{Cestode} tape worm, Dibothrio cephalus latus, in the intestine. The writer has also observed a similar anaemia in Chinese suffering from infection with the trematode Clonorchis Sinensis which is found in the intestine and attacks the liver and pancreas. Now in sprue the liver, pancreas and intestine all show evidence of disease and pernicious anaemia is the result. It certainly makes one think that the origin of true pernicious anaemia might possibly be found in the intestine.

As to the origin of sprue, Sir Leonard Rogers thinks that it may be due to the fact that vitamins are not properly digested. By far the more generally accepted theory is the infective theory. Manson Bahr thinks it may be due to the Monilia Albicans or thrush fungus. The overgrowth of the mouth and tongue with the thrush fungus, however, may be the terminal event in other chronic and wasting diseases, such as phthisis, /

DIPHYLLODIBOTHRUM
LATUS

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phthisis, carcinoma and diabetes. Therefore the overgrowth of the intestinal canal, in sprue, with these yeasts may be regarded merely as the result of a secondary infection in a debilitated subject.

The writer has been treating cases in Hong Kong for the last 5 years. He started with the recognised remedies, such as yellow santonin, liver soup, sour milk and various meat and fruit diets, but although most of them seemed to give temporary relief, in no case was the cure permanent. Then came Scott's discovery of the calcium and parathyroid treatment.

The writer used this treatment exclusively for a time and the results showed a great improvement on the old methods. Still, even with this method of treatment, there were a certain number of cases that showed no improvement and a few cases which relapsed from 6 - 18 months after cessation of treatment. In searching for a remedy for these cases the writer first tried raw liver. This caused definite improvement in 2 cases, but difficulty was experienced in getting patients to take a sufficient quantity. As may be imagined raw liver in the tropics is far from appetising. The next step was treatment with dried liver. This proved excellent and apparently produced a cure in 2 cases which had not relapsed 2 years after cessation of treatment. While experimenting with this treatment, the writer came across a French proprietary preparation/

preparation called "Pancrepatine". This contains extract of liver and extract of pancreas in keratin coated capsules. It has been used in France for the treatment of diabetes. Now in sprue there is both liver and pancreatic deficiency and treatment with this preparation immediately suggested itself especially as the substance was in capsules which prevented alteration by the gastric juices. This treatment may sound rather symptomatic, but it has yielded excellent results in 6 cases, who have been under observation from 18 months to 2 years. The period of observation is not long enough to claim a cure, as cases may recur after a period of twenty years without symptoms. What can be claimed, however, is that these cases, who were faced with no alternative but to leave the tropics, have been enabled to stay there and enjoy good health, while carrying on their work.

HISTORICAL SURVEY.

In 1737 a disease resembling Sprue was described by Bricknell.

In 1766 Hillary described a similar condition in an article, "Observations on the changes of the air and concomitant epidemical diseases in the Island of Barbados". He called it "Apthoides Chronica".

In 1835, 1854 and 1857 Twining, Grant and Cunningham described it occurring in India.

The earlier writings of the Indian Army surgeons of the nineteenth century, made frequent allusion to forms of chronic diarrhoea so prevalent in that country, but no reference is made in any of them to the oral symptoms which are so characteristic a feature of this disease.

In 1864 and during the twenty years following, several French writers noted its appearance in Cochin China. The first accounts of sprue, as a separate entity, distinct from dysentery, were written quite independently of one another by Van der Burg in Botavia, Java, and by Manson in Amoy, China in 1880. Van der Burg called it "Indische Spruw" and Manson anglicized the name into Sprue.

In 1881 Sir Joseph Fayrer delivered the Lettsomian Lecture on "White Tropical Diarrhoea".
In/

In the same year an editorial in the British Medical Journal discusses sprue. It is reported to be invariably fatal, if the sufferer remains under conditions in which the disease was acquired and is ascribed to the general unsuitability of the European constitution to tropical climates. Long continued residence in high temperature is looked on as the most powerful influence in aggravating the disease. Treatment is stated to be of little avail and the only remedy recommended is to leave the tropics. The editor puts forward the suggestion that sprue is a form of idiopathic or progressive pernicious anaemia. It is of interest to note that 47 years later the comparison of sprue and pernicious anaemia is still being discussed.

The symptoms described by the early writers vary little from those met with nowadays. Ever since the earliest reports it has been recognised as a clinical entity, separate from other diarrhoeas. The name may have varied, but the condition described has been always the same.

The writer has enquired from native doctors, trained in Chinese medicine, if they recognised the disease. These doctors are often extremely observant men but none of them had recognised it nor had they read of any combination of symptoms, resembling sprue, in their books.

Thin contributed a number of papers to the medical journals from 1883 onwards, characterised by great accuracy of observation and especially detailed attention to diet and treatment. All these he embodied in a volume with the title of "Psilosis or Sprue", which he published in 1897. French writings on this subject all emanate from Cochin China and are mainly concerned with pathological studies (Kelch and Kiener (1884), Bertrand and Fontan (1886)). These latter authors describe the disease as "Entero-colite Endemique des Pays Chauds", by which synonym it is still known in France. In 1906 there appeared a valuable summary of our knowledge on this subject, in the Dutch language, by Rademaker. A very full and complete modern account is a monograph by Carnegie-Brown, published in 1908.

Since then the disease has been described by many workers and the late war brought physicians into contact with cases in this country.

Various theories have recently been put forward as to its etiology, one being that it is identical with pernicious anaemia. Great strides have been made in treatment and many experiments done in this direction.

EPIDEMIOLOGY AND AETIOLOGY.GEOGRAPHICAL DISTRIBUTION.

Sprue is not essentially a disease of the tropics but it has a well defined geographical distribution. The majority of cases in Europeans come from India, Ceylon, the Malay states, Java and China. A few cases in Europeans have been reported from Central Africa. Sprue is a disease, with such insidious onset and with such indefinite symptoms, that it is apt to be overlooked by practitioners without experience of tropical disease. It may be confused with pellagra with which it has some symptoms in common and also with chronic amoebic dysentery. When it becomes better known it may be found that it is more widely distributed than reports have shown. It has been reported from Burma, Siam, Cochin China, Japan, Sumatra, Celebes, Macassar, Borneo, the Philippines and Mecca. In Australasia it occurs in Queensland, the Northern Territory of Australia and Fiji. In Africa, isolated cases have occurred in Morocco, in the Gold Coast and Upper Congo. In the New World, it is found in the Southern States, Haiti, West Indies, Mexico and South America. Ashford has reported many cases from Porto Rico. In Europe cases have been recorded in Sicily and Southern Italy. Manson Bahr has /

has reported one case in a woman who had never been out of England. A case has been reported recently from Denmark, in a woman who had never left the country, but from the description of the case it is doubtful if it was true sprue.²

The distribution is more regional than climatic. It has come to be regarded as a disease which pre-eminently affects Europeans. This may be due to the difficulties of diagnosis among natives and possibly to the fact that the disease occurs in a milder form in them as a result of a certain amount of racial immunity. Most natives of tropical countries have suffered from various forms of diarrhoea, at one time or another, and many are anaemic as a result of the ravages of Malaria and Hook worm. In some countries the habit of betel chewing stains the buccal mucosa bright red, which would tend to mask any tongue lesions which might be present.³ Van der Burg stated that it is definitely a disease of the natives in Java, while Van der Scheer has estimated that, as compared with Europeans, the dark races were by 30% less liable to the disease. Manson Bahr has recorded cases in Moors, Sinhalese and Indians during his researches in Ceylon in 1912.

In a disease with such an insidious onset, it is difficult to say that there is any seasonal incidence.

In/

In countries with a hot and cold season, cases undoubtedly do better in the cold season, especially if that is also the dry season. It would appear that a hot, damp climate is most unfavourable to the sufferer from the disease.

AGE AND SEX INCIDENCE.

Middle aged and elderly persons are most liable to be attacked but it may occur in children. Van der Burg claimed to have recognised it in an infant of one and a half years. The female sex is more prone than the male to the development of the disease. This is borne out by the figures of Manson Bahr, in which, out of ³ 36 cases of sprue in Europeans, 19 were female and 17 males. The greatest liability of the female is more evident when it is remembered that in Ceylon, when the observations were made, the proportion of males to females, in the European community, was almost as two is to one.

PREDISPOSING CAUSES.

Unhealthy surroundings, insanitary conditions and poor water supply have been put forward and these may, by reducing resistance, predispose to the development of the disease. There is a popular idea, in Ceylon, that people, who live in houses in which the beams have been attacked by dry rot, are more/

more liable to sprue. There is no real evidence to substantiate this however. Previous disease certainly seems to predispose to it, especially diseases affecting the intestinal canal, such as amoebic dysentery, bacillary dysentery and hill diarrhoea. It may appear in women, after child-birth or prolonged lactation. Of all the predisposing causes, long residence in the endemic area is the most important, and the individual who has been in the tropics over 15 years is most liable to be attacked.

AETIOLOGY.

Sprue belongs to the class of Tropical Diseases of which the aetiology is unknown. Many theories have however been advanced as to its cause.

1. Kohlbrugges Theory that it is due to a yeast fungus, *Parasaccharomyces Ashfordi* or *Monilia Psilosis*.

In 1901 Kohlbrugge found in the intestinal mucus in the epithelial covering of the tongue and of the oesophagus large numbers of yeast cells resembling the thrush fungus, *Monilia albicans*, but he found similar organisms in the faeces of normal individuals.

These observations were confirmed in papers in 1902 by de Haan, in 1905 by Van der Scheer, in 1908 by Le Dantee and in 1909 by Macey.

In/

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In 1913 Manson Bahr cultivated yeast cells and mycelial elements from the tongue, oesophagus, stomach, intestines, spleen, liver and kidneys at sprue post-mortem. He also cultivated the same organisms from the saliva and stools during life. These yeasts belong to the genus *Monilia*, but culturally could not be distinguished from the *Monilia albicans* or thrush fungus. He gave the following reasons for concluding that this fungus is the cause of the disease:

- (1) Its almost constant presence in large numbers in the tongue, saliva, intestinal mucus and stools of sprue patients and its rarity in the stools of normal individuals or those suffering from other forms of diarrhoea.
- (2) The gaseous stools of sprue can best be explained by the presence of these gas forming organisms and their proclivity to ferment the carbohydrates, with acid and gas formation.
- (3) The presence of mycelial elements in the epithelium of the tongue and their power of causing necrosis and exfoliation of the stratified cells.

More evidence in favour of a blastomycotic infection has been accumulated by Ashford¹ in Porto Rico. He claims that the *Monilia* in question belongs to a distinct species separate from the thrush fungus (*M. Albicans*) and proposed to name it *Monilia Psilosis*.
Out/

Out of 1435 cases of sprue, 1202 or 83.7%, were positive, mycologically, serologically, or both, for *Monilia Psilosis*. Out of 698 cases clinically free from any suspicion of sprue, he distinguished 1.2% carriers of the fungus.

Anderson (1917) in an exhaustive inquiry, conducted in the Department of Plant Pathology of the University of Illinois, concluded that yeast-like fungi are commonly found in the intestinal tract of man. Many species are ingested with the food and the varieties commonly present in nature are known as "wild yeasts". The pathogenic yeasts obtained from sprue he found were similar to those of Ashford and were easily distinguishable from the wild varieties, but were similar in many characters to the *Monilia albicans*. Anderson therefore proposed to name the organism *Parasaccharomyces ashfordi*. Ashford claims that cultures of his *Monilia*, when injected into the tongue of rabbits produce a gaseous diarrhoea, gradual emaciation and death. They are intensely toxic to white rats when injected intraperitoneally.

Using emulsions of *Parasaccharomyces ashfordi* as an antigen, Martinez and Michel, in 1916, have been able to produce a satisfactory complement deviation with the sera of 400 cases.

Fisher claims to have produced sprue by feeding white mice and monkeys on cultures of *Monilia*.

Baumgartner/

Baumgartner and Smith⁵ (1926) in a series of eleven cases found *Monilia* in the faeces of every one. In blood cultures a negative result was obtained. They feel sure that the *Monilia* is more than a secondary invader.

Fairley and Mackie, (1925) at Bombay, investigated 150 strains of yeasts obtained from sprue cases and others. They consider the classification of yeasts to be in a chaotic state. They point out that yeasts of the typical *Monilia Ashfordi* type are only found in about half the cases of sprue and are present in non-sprue cases and in healthy persons to the same extent. A series of experiments to produce sprue in monkeys by feeding was frustrated by the discovery of a yeast of the *Ashfordi* type in their faeces. They consider that evidence that any yeast plays a specific rôle, in the etiology of sprue, is definitely lacking.

⁷ Nicholls, (1918) in India, failed to grow yeasts in culture media, inoculated with scrapings from tongue and mouth, in 50% of sprue cases among Europeans.

The *Monilia* theory seems to have been strongly supported by a small body of enthusiastic workers, but more recent research has failed to confirm it. Probably these organisms grow in the stools, after a primary cause has weakened the digestive and absorptive functions of the intestinal canal. The bacterial fauna /

fauna of the faeces is altered in most diseases of the intestines, notably typhoid and dysentery, and this is probably the case in sprue. The overgrowth with the thrush fungus may be the terminal event in any chronic wasting disease. It is unlikely that it is the primary cause of sprue, but it might however be the cause of some of the secondary symptoms.

2. Food Deficiency Theory.

The theory that sprue might be due to a deficiency of essential food factors was supported by Cantlie and there are still those who would include it among diseases due to a vitamin free or deficient diet. McCarrison fed monkeys upon a vitamine free diet and produced a condition greatly resembling the intestinal lesions of sprue as seen in man. In Pellagra, which is considered by many authorities to be a deficiency disease, there are many symptoms similar to those found in sprue. The theory that sprue is a deficiency disease, pure and simple, is hardly tenable as many Europeans attacked by it are in affluent circumstances. Again, in countries where sprue is not endemic, deficiency of the essential food factors produces no condition like sprue. The writer has known of cases of sprue cured simply by residence in a different climate without medicine or change of diet.

Sir/

Sir Leonard Rogers⁸ thinks that there is a strong evidence for the belief that deficiency in vitamins is a predisposing cause of sprue. He states that a diet of marmite and tomatoes gives good results, although marmite is an extract of yeast, the very fungus which is supposed to cause sprue. He is of the opinion that it might be due to the fact that vitamins were not properly digested, rather than to any lack in the diet.

Nicholls⁶ thinks that possibly the absence of a vitamin from the food renders the body less capable of resisting a streptococcal infection.

Smith⁹ states that the pathogenicity of *Monilia Psilosis* appears to be very slight, except in a suitable soil, which appears to be an avitaminosis, or a calcium deficiency dependent on excessive fat or protein dietary.

Scott¹⁰ states that a lack of calcium when vitamins are supplied induces the same changes in the endocrine glands as are seen in conditions where calcium in the diet is abundant, but vitamins are deficient. In this way he connects the food deficiency theory with the calcium deficiency theory.

As a predisposing factor vitamin deficiency might play a part in the cause of sprue, but, apart from that, there is no direct evidence that it is a primary cause.

3. Scott's Theory of disturbed Calcium Metabolism. ¹⁰

The idea was suggested to Scott by the symptoms of a sprue patient who suffered greatly from carpo-pedal spasms and cramps. The association of carpo-pedal spasms with calcium deficiency had been known for some time. The correlation of these with the diarrhoea and intestinal toxins might be referred to the group of organs which have been credited with the control of both these conditions, namely, the parathyroids. These are believed to have a two-fold function, the regulation of calcium metabolism and of detoxication, in particular of the poisons of intestinal origin. In addition to this, but as subsidiary and not acting in all cases, is the condition of hyperchlorhydria. If this is present we may have as a result the excessive production of secretin by the action of the acid of the gastric juice upon the pro-secretin of the mucous membrane of the duodenum.

Excess of secretin leads to stimulation of the pancreas with an increased splitting up of fats, so that the normal ratio of neutral fats to fatty acids is diminished. When the European goes to the East, his diet is in several ways unnatural. He often takes more highly spiced food and more alcohol and hyperchlorhydria is common. The food and methods of cooking lead to an increased ingestion of fats. Many observers have noticed that in children to whom an excess of fats was given, the retention of calcium was /

was reduced. This they explained by the increased formation of calcium soaps in the intestine, unabsorbed fatty acids being eliminated in the stools as soaps of potassium, sodium and calcium, leading thereby to the impoverishment of the body in respect of bases. Again Korenchevsky found that in animals on a diet deficient in calcium, diarrhoea was noticed, together with loss of weight and increased nervous excitability. The amount of calcium in the blood does not depend solely on the amount of calcium salts ingested, but on the efficiency of the calcium regulating mechanism - the parathyroids. The mechanism of this regulation would be upset if the toxins were more than could be dealt with, and the absorption of certain toxins seems to lead to such disturbance. The ionic calcium suffers diminution and becomes relatively deficient first, while in the later stages there is an absolute deficiency. Calcium deficiency is therefore regarded as an indication of toxic absorption. In cases of sprue there may be one of two conditions. In the one, where fats are in excess, there is an excessive excretion of calcium, in addition to intoxication of intestinal origin; in the other protein excess with intestinal toxin formation. In both, the parathyroid detoxicating function is overburdened, with a resultant disorganisation of its calcium regulating function. There may be, in addition, diminished/

diminished calcium absorption. Both functions, therefore, of these glands are interfered with.

From the point of view of aetiology this theory gets no nearer the primary cause of the disease. Scott merely demonstrates how the symptoms found in sprue may be caused by a poison acting in the alimentary canal. What that poison is, or where it comes from, does not enter into the argument. From the point of view of treatment, however, this theory has led to a great advance over previous methods.

4. Theory that Sprue and Pernicious anaemia are the same disease.

Reed and Wyckoff, in 1926, wrote a paper,¹¹ to show that a common clinical entity is embraced by the diseases commonly diagnosed as tropical sprue, pernicious anaemia and subacute combined degeneration of the spinal cord. A study of published cases leads the authors to think the three may be due to different manifestations of a common toxin and that this toxin attacks the three systems - the blood, the gastrointestinal tract and the nervous system - in varying degrees. For example, typical sprue may show evidence of cord changes and pernicious features in the blood, while typical Addisonian anaemia shows evidence/

evidence of sprue-like gastro-intestinal changes and of cord degeneration. Subacute combined degeneration of the cord is always associated with progressive anaemia which tends to become pernicious in character, frequently with achylia and other gastro-intestinal lesions. It is suggested that the toxin is most likely a group or type toxin and that it originates from the intestinal canal. The evidence they cite is best set forth in the sub-joined table:-

	Sprue.	Pernicious Anaemia.	Combined degeneration.
Insidious onset.	+++	+++	+++
Periodicity	+++	++	Improves as anaemia improves.
Stomatitis	+++	++	+
Achylia	++	+++	+
Gastro-intestinal atrophy.	+++	++	+
Diarrhoea, nausea and vomiting.	+++	++	+
Anaemia:-			
Secondary type	+++	+	+
Later pernicious	++	+++	+++
Fever	0	+	+
Fatal when established	++	+++	+++
Cord symptoms	+	++	+++
Complexion	muddy	lemon	biscuit.

Newham and Morris¹² (1926) believe that sprue and Addisonian anaemia, though having several features in common, are distinct clinical entities. They point out that sprue is definitely a disease of the tropics, in some way connected with exposure of susceptible individuals to conditions inseparable from life in a tropical climate, Central Africa excepted. The typical anaemia which accompanies the two diseases is almost identical, but this alone does not indicate a similar aetiology. Addisonian anaemia is generally a fatal disease, sprue by no means so. The toxin of Addisonian anaemia has a most definite selective action upon the peripheral nerves, an effect which is not found in sprue.

Wood¹³ (1925) regards the nervous changes in sprue as a point of distinction. He has discovered the *Monilia Psilosis* in the faeces of 15 cases of pernicious anaemia.

Many writers during the last two years have compared the two diseases without coming to any definite conclusions. One point of difference which does not appear to have been noted is the disturbance in pancreatic function in sprue. This does not occur in pernicious anaemia and may be of significance. Also the carpo-pedal spasms and cramps of sprue are not found in pernicious anaemia. If estimations of the/

the blood calcium were done in pernicious anaemia that too, might help to separate the two diseases.

Because there are many symptoms common to pernicious anaemia and sprue, there is no reason to infer that they are caused by the same organism or poison. The symptoms of amoebic dysentery and bacillary dysentery may be almost identical, but it is well known that they are caused by totally different organisms acting on the same part of the intestine. Again the parasite bothriocephalus latus may cause a condition similar to pernicious anaemia, but no one suggests that pernicious anaemia is due to this organism. One point however stands out. Invasion of the intestine by bothriocephalus, hook worm or Clonorchis sineusis has caused an anaemia of the pernicious or sprue type, therefore it is only reasonable to suppose that sprue and pernicious anaemia are caused by other organisms, not necessarily the same but acting on the same part of the intestine.

5. Bacterial Theory that it is caused by a Streptococcus.

Sir Leonard Rogers¹⁴ in 1914 made cultures from the mouth lesions of 2 cases. These gave a pure growth of streptococci which were injected as a vaccine in doses of from 50-100 million once a week.

Rapid/

Rapid improvement of symptoms was noted. He considered that this opened up an interesting and suggestive question as to the rôle played by this organism in the disease, at least in some cases. Four years later he published another article¹⁵ on the treatment of 17 cases with autogenous oral streptococcal vaccines and claimed marked benefit in every case. He considers that these results confirmed his view that sprue is essentially a streptococcal infection originating in the mouth and spreading down the intestinal canal.

Nicolls¹⁶ (1919) wrote confirming Rogers results. He inoculated culture media with scrapings from tongue and mouth of cases of sprue. In 50% he was unable to grow yeasts, but in every case he succeeded in isolating streptococci. He treated cases with autogenous streptococcal vaccines with favourable results. He points out that sprue is almost confined to thickly populated countries in which the climate is humid and warm. The inhabitants of India are addicted to the habit of spitting and there is every chance of streptococci being continually passed from one to another. He cannot distinguish the streptococcus found in sprue from the streptococcus viridans of the normal mouth.

Many others have claimed success with many different strains of autogenous vaccines. Possibly they all did good as they came from secondary organisms which/

which although not primarily causing the disease, gave rise to secondary symptoms. The streptococcus viridans is present in almost every saliva, also on all buccal ulcerations whether associated with sprue or not. The difficulty of avoiding extraneous organisms in such a septic cavity as the mouth, renders the recognition of the organism involved an especially difficult one. Any claim, therefore, that the streptococcus is the cause of the disease requires considerable substantiation.

6. Lymphatic Obstruction a factor in Sprue.

Jones¹⁷ wrote in 1924 from Bombay that two cases of Sprue were operated on for acute appendicitis. The ileum was seen to be attenuated, while distension and varicosity of the lacteals, in the mesentery attached to the jejunum, were very apparent. No evidence of intestinal ulceration was obtained. This condition had never been previously observed in his considerable experience of abdominal surgery and might shed some light on the aetiology of sprue. Delay in the lymph flow probably takes place in the sclerosed lymph glands in the mesentery. Lymphatic obstruction may be the predominant factor. It is conceivable that the continuous absorption of toxin, from the intestinal mucosa, will eventually produce sclerosis of the mesenteric glands and so cause lymphatic obstruction.

The/

The writer has operated for appendicitis on one case of sprue and failed to note the appearances referred to by Jones.

Writers in the old days put forward many theories which are now discredited. The amoeba histolytica was at one time put forward as the cause. It is now known that it is not connected with sprue except perhaps as a predisposing factor.

From a review of these possible causes of the disease, it would appear that there is much to be said in favour of the infective theory. Calcium deficiency might be brought about by the action of micro organisms on the intestine causing the absorption of poisons and interference with calcium metabolism. Vitamine deficiency might be accounted for in the same way, also involvement of the lymphatics which is the natural sequel to any infection. In attempting to prove that the *Monilia psilosis* is the causal organism, the same difficulty occurs as with the streptococcus, namely that both are found as non-pathogenic inhabitants of the alimentary canal. Many infective diseases are known which are improved or cured by transference of the patient to a suitable climate. In this respect sprue is outstanding, and it seems natural to infer that it is caused by an organism, which has not the same chance of flourishing, when the patient is removed from the endemic area.

P A T H O L O G Y.1. GENERAL PATHOLOGY.Morbid Anatomy.

In many of the published descriptions of the morbid anatomy of sprue not enough regard seems to have been paid to the extremely rapid changes which take place in the intestines after death in the tropics, especially changes in such a delicate structure as the intestinal mucosa. Many changes formerly described, such as the complete loss of epithelium and absorptive villi of the small gut, may be in part due to decomposition.³

The bodies present the appearance of long continued starvation. There is consequently a complete absence of subcutaneous or visceral fat. The muscles are dark brown in colour and very dry; the heart is in a condition of brown atrophy. All the organs are similarly wasted and may weigh less than half the normal amount. This atrophy is especially visible in the case of the liver. In colour, the liver has a yellow tint due to excessive fatty changes. In some cases however it has a greenish hue due to staining with biliverdin.

The Pancreas is small and atrophied and by some investigators/

investigators it is said to show fibrotic changes. The spleen to the naked eye shows no change.

Histology.

Sections of the liver show extensive fatty changes in the cells at the periphery of the lobules and decomposition of haemosiderin granules. The spleen shows a similar deposition of the pigment in the pulp cells, as well as extensive hyaline changes in the endothelium of the venous sinuses. One of the most striking features is the accumulation of spherical masses of hyaline in the splenic pulp. These stain an intense purple with Weigert and are apparently identical with Russell's bodies which have been found in neoplasms of various kinds.

Sections and other preparations of the red bone marrow show no evidence of an erythroblastic response such as is described in pernicious anaemia.

No histological change has been described in the pancreas or kidneys.

No account appears yet to have been written of the degenerative changes in the spinal cord. Clinical evidence in a few cases points to degeneration in the posterior and lateral columns.

2. LOCAL PATHOLOGY.Morbid Anatomy.

The tongue looks bare and raw especially at the edges. It may be covered at the tip and margins with small blisters or apthae. These may also be present on the fraenum, the buccal mucosa and inside the lower lip. There may be great atrophy of the filiform papillae leaving the fungiform papillae standing out very distinctly. The tongue is often covered with a thin film of the thrush fungus. The oesophagus may be covered with a yellowish membrane composed of an overgrowth of the Monilia. The stomach is small and contracted and the mucous membrane shows evidence of chronic inflammation. The thrust fungus may also be present here. In some cases the stomach appears to be normal.

The most noticeable feature in the abdomen is the transparent and distended condition of the ileum. On section this is found to contain no intestinal contents, but a considerable amount of gas, and the mucous membrane to be covered with a layer of viscid mucus. No deep ulceration of the mucus surface is generally found in either the small or the large gut, though a few superficial follicular lesions may be present in the lower part of the ileum.

Manson Bahr (1924)¹⁸ describes the autopsy of two rapidly/

rapidly fatal cases. Both died of peritonitis from perforation. The main interest centred in the ileum. The mucous membrane was acutely inflamed with diaphanous transparent patches. Ulcers of varying sizes were situated on the surface opposite the peritoneal attachment. They were separated from each other at regular intervals of about 9 inches. These ulcers were more or less of the same size, roughly oval in shape, with puckered rolled margins and haemorrhagic bases. In all of them actual perforation of the bowel had occurred. In size, they varied from .5 + 1 cm. The ulcers had no relation apparently to Peyer's patches, which were normal in appearance. No fungi were found in these cases, though cultures were made from all the organs, as well as the intestine.

Justi¹⁹ and Fischer and Von Hecker²⁰ have also published autopsies in which ulceration of the small gut was found.

The large intestine is thinned but does not show such marked signs of inflammation and ulceration as are found in the small intestine. The anus may show signs of excoriation from the irritation of the acid stools.

In one reported case²¹ the lymph glands of the mesentery were large and congested.

Histology.

In sections of the tongue considerable desquamation of the stratified epithelium, especially of/

of the fungiform papillae, can be demonstrated. Clumps of yeast cells may be visible lying between individual papillae. Sometimes a downgrowth of mycelial elements through the corium into the muscular fibres can be seen. Immediately surrounding these downgrowths, there is considerable tissue reaction, as evidenced by accumulation of polymorph cells, by dilatation of the capillaries and by round celled infiltration in the deeper layers. The same changes are visible in the oesophagus. Throughout the whole length of the tube there is evidence of desquamation, of partially necrotic stratified epithelium over considerable tracts. On the surface layers are to be seen the vegetative yeast cells, while extending down to the basement membrane are mycelial threads. Subacute inflammatory changes can be demonstrated in the areolar coat. The presence of yeast cells and mycelium in the tissues can best be demonstrated in sections stained by Weigert's method. Yeast cells are present in numbers in the stomach mucus. The mucoid secretion throughout both large and small intestine shows an abundance of these cells. These changes in the tongue and oesophagus do not differ materially from those seen in emaciated children dying with a terminal thrush infection.

Sections of the stomach appear to be normal, but the intestinal canal, from duodenum to rectum, exhibits /

exhibits changes indicative of a chronic inflammation. In the ileum the villi are quadrangular in shape and shrunken; the columnar epithelium is for the most part preserved but the cells themselves stain imperfectly and the goblet cells are distended with mucus secretion. Chronic inflammatory changes are evident in the congestion of the capillaries and in the infiltration of the interstitial tissues with lymphocytes and plasma cells. There are similar subacute inflammatory changes in the sub mucosa, with small celled infiltration round the dilated nutrient blood-vessels. There are also extensive fibrotic changes in the submucosa, as evidenced by the presence of collagenous fibres. In the tissues underlying ulcers, numerous granular masses of yellowish brown pigment (haemofuscin) are found.¹⁸

3. CLINICAL PATHOLOGY.

The Stools.

The most important features of the sprue stools are their colour, their size and chemical composition.

Colour. It was formerly thought that the large and frothy stools, passed in the early stages of sprue, were abnormally rich in bile; but as the disease progressed these elements became reduced in amount /

amount and eventually were absent from the stools altogether. To this the peculiar pale or clay-like colour of the stool was ascribed. It has been proved, however, by Sidney Martin and Blyth, that the bile pigment of the stools (hydrobilirubin) is present in reality, but in the form of a colourless compound, leucobilin, a reduction product of hydrobilirubin.

A similar chemical reduction of the pigments would appear to take place in certain diseases of the pancreas, such as malignant disease, in which the pancreatic juice is absent.

It is now generally recognised that it is to this factor, as well as to the abnormal proportion of crystalline fats, that the pale colour of the sprue stool is to be ascribed.

If an extract be made with 90% alcohol of an almost colourless sprue stool and the filtrate exposed to the air, a white colourless fluid results, which slowly becomes oxidised into a yellow colour and gives the spectrum of hydrobilirubin.

That bile is excreted from the gall bladder, in sprue, is evident from the fact that abundant, amber coloured bile can be found post-mortem.

Morris²² (1926) uses the German name urobilin for hydrobilirubin and for leucobilin, the reduced colourless product, he uses the name urobilinogen. He shows how the amount of blood destruction going on/

on can be calculated from the daily amount of urobilin excreted. The severer the anaemia, the greater is the amount of urobilin excreted.

This change in the bile pigments may be the explanation of the colour of sprue stools, but the well known experiment of Hermann must be kept in mind. This matter of the Hermann isolated loop of intestine and its secreted faeces is one of great difficulty. Starling²³ also states "After some weeks an isolated loop (of intestine with full blood supply) will be found to contain a semi solid material similar to faeces in appearance, consistence and chemical constitution", on which experiment is based the statement, in many physiology books, that the normal colour of faeces has no relation to the presence of bile pigments and their products.

Size of Sprue Stools.

The large size of the stool is one of the prominent symptoms and naturally varies with the amount of undigested food residue passed.

The average daily weight of a normal stool, when the patient is on a milk diet, is estimated at 6 oz. and according to Harley 87% of the amount of solid matter ingested in the food is normally absorbed. The size of the individual sprue stool varies enormously. Daily stools up to 31 oz. have been recorded. Analyses of these stools, as compared with the amount of/

of solid matter ingested, point to the fact that, even in cases which are progressing favourably, on a milk diet, less than 60% of the solid matter is absorbed.

Chemical Composition of Sprue Stools.

The amount of fat in the stools is greatly increased. According to analysis the amount of fat passed in normal faeces averages about 3.75 gm. per diem, when the diet consists solely of milk, that is to say that the fat absorption in the normal subject is over 95% of the total amount ingested. With a similar diet the excretion of fat in sprue averages about 35 gm. daily. The total fat may amount to from 25-50% of the dried stool.

The analyses of sprue stools were undertaken by Thomson²⁴ (1925) to ascertain if the pancreas played any part in the disease. The proportion of neutral fat to fatty acid in normal stools remains practically constant in the ratio of 1 : 2. The organ chiefly concerned in the splitting of neutral fats is the pancreas. In pancreatic deficiency the proportion of neutral fat to fatty acids in the stools is increased - in extreme cases it may be 10 - 1. In sprue stools the proportion is reversed and there is a relative increase in the fatty acids. The proportion of fatty acids to neutral fat may be as high as 8 : 1. This/

This excessive splitting up of the fats would appear to be due to excessive activity on the part of the pancreas, but Thomson, by means of Einhorn's tube, examined the duodenal juice and found that to be normal in all three ferments diastase, trypsin and lipase. Scott¹⁰ on the other hand claims that there is over stimulation of the pancreas with excessive secretion caused by the hyperchlorhydria.

Van Steenis²⁵ (1926) with the duodenal tube found the secretion of the pancreas to be normal. He found there was a lowered secretion of bile and assumed that the absorption of fats was hindered by the absence of bile.

Newham²⁶ (1926) from analyses of stools from 11 sprue patients stated that the biliary functions are deranged and there is a diminished output of cholesterol.

Fairley and Mackie⁶ (1926) state as regards the fat analysis of faeces, in early cases their findings suggest a failure of pancreatic functions. In an examination of the blood they found the total fat to be below normal and they consider that the question arises whether the increased fat content of sprue stools may not be partially dependent on excessive excretion of fat through the intestinal mucosa.

Silverman and Denis²⁷ (1923) give their results of tests of the duodenal contents for enzymic activity. They/

They state that attempts at testing the faeces for ferments should be discouraged since this method of analysis is inaccurate. The duodenal tube is the only method of finding the true activity. They find enzymic activity definitely diminished. After treatment with calcium and pancreatin they re-examined the respective ferments and found their activity greatly increased. They consider that these facts encourage the belief that in sprue the pancreas does not always undergo extensive or permanent damage.

Manson Bahr³ states that his researches point to a diminution of the pancreatic ferments.

The evidence of all these reports is very conflicting. Is there or is there not a pancreatic deficiency? The writer is of the opinion that there is an over stimulation of the pancreas in the early stage of the disease and the result of this is an impairment of function in the later stages.

The reason for this may be that in the early stages there tends to be an excess of free HCl in the stomach. This may stimulate the pancreas unduly. In the well established disease the stools contain a larger percentage of fat, indicating a failure on the part of the pancreas; also there are some cases which are greatly benefitted by the administration of pancreatic extract. That the pancreas is not seriously/

seriously damaged is indicated by the fact that when a case recovers the pancreas regains its full function.

The reaction of the stools is almost invariably acid and is apparently due to the amount of lactic and butyric acids present. These possibly account for the peculiar sour odour which is a characteristic of sprue.

There seems to be a deficit in the fermentation and absorption of the carbohydrates. In the constipated sprue stool mucus may be present. It does not as a rule contain any pus cells or indications of intestinal ulceration.

The Urine passed is normal in amount and specific gravity. Its reaction is invariably acid.

The daily excretion of urea is lower than in the normal subject. Urobilin and indican are generally present. The urine of sprue is said to give a positive Cammidge's reaction, a further indication of pancreatic insufficiency. Manson Bahr³ states that in urines he has examined he is unable to substantiate this point. Thomson²⁴ states that the diastolic reaction of the urine is on the low side.

A substance which reduces Fehlings solution and is certainly not glucose has been recorded by Halberkann. The writer has also met this phenomenon in very severe cases.

Saliva. This is invariably acid and may contain yeast cells.

Gastric juice. Free hydrochloric acid is frequently in excess in early cases. In advanced cases it may be absent.

The Blood.

A grave degree of anaemia is found only in the most advanced stages of the disease. In the earliest stages, there appears to be no alteration in the red or white cells or in their relative proportions. When the symptoms are established there is a slight anaemia of the aplastic type. In the cachectic stage the anaemia is severe. The number of red cells has been recorded as low as 960,000 per ccm. with a haemoglobin percentage of 20. The colour index is generally raised and may be about 1.5. In other respects the blood picture resembles that of pernicious anaemia of the aplastic type. Nucleated reds are rare and the blood platelets seem to be reduced in number. Alterations in the shape and size of the erythrocytes, (poikilocytosis and anisocytosis), together with megalocytosis and rarely polychromatophilia are met with. Thus there is no evidence of any sustained erythroblastic response. There is a tendency to leucopenia in the terminal stages together with a relative increase in the lymphocytes.

There /

There is little evidence for regarding the anaemia of sprue as being due to a primary blood infection. It is probably due to the absorption of some blood destroying toxin from the alimentary canal. Anaemia is not invariably present even in advanced and fatal cases. The course of the anaemia is dependent on the response to treatment of the sprue.

Cholestrol content of blood. In eleven cases of sprue, investigated by Newham¹² and Morris, there was a definite hypocholestraemia. In this feature there is no distinction between it and pernicious anaemia.

As regards blood grouping the majority of cases belong to Group IV.

Calcium content of blood. Scott¹⁰ has shown that there is a definite calcium deficiency. First the amount of free calcium is reduced by being transformed into combined calcium. Later the total calcium is reduced. The following table shows the changes which take place:-

	Free Ca.	Combined Ca.	Total in mg. per 100 cc serum.
Normal (after clotting)	10.7	0.0	10.7
Severe case.	6.1	3.8	9.9
Average case.	7.	2.9	9.9
Mild case.	8.	2.	10.

CLINICAL MANIFESTATIONS.ONSET OF SYMPTOMS.

As a rule the onset is very insidious. Cases starting acutely probably belong to those in whom the disease has been lying latent for some time and some secondary factor, such as dysentery, suddenly precipitates the onset of symptoms. The earliest symptoms vary greatly in different patients. Diagnosis should not be postponed till the typical, white, gaseous stools develop, for this represents the well established disease. Hospital records go to show that patients are frequently admitted with diagnoses of debility and enteritis, before some classical feature of sprue develops. Some writers state that sprue very rarely develops in healthy persons. This is probably accurate in as far as the sprue has been undermining the patient's general health for weeks, perhaps months, before the onset of symptoms. A looseness of the bowels, with 3 or 4 motions a day, may be the only initial symptom. This may last 2 or 3 days. The patient probably takes a dose of castor oil and the looseness disappears. These early motions have no characteristic feature. They may be greenish, or brown, in colour and/

and are seldom of the pale colour to be seen later on in the disease. At this stage there are no mouth symptoms or any other symptoms, except, perhaps a change in the patient's mental outlook. He may become irritable and apprehensive for no reason known to himself. People, who were formerly cheery, may become dull and morose. This mental condition is a well marked feature of sprue.

Weeks or months later the diarrhoea again returns. In the meantime the patient may have suffered from dyspepsia, with hyperchlorhydria, which he in no way connects with his diarrhoea. This time he probably consults a doctor who may, or may not, examine the stools for amoebae. As often as not the patient is given a dose of castor oil and a few injections of emetine, on the off chance that he is suffering from chronic dysentery. The patient may be put on a milk diet for a few days and the diarrhoea clears up again. In the meantime he steadily loses weight. From now onward the patient may complain of an increasing irregularity of the bowels. He volunteers the information that he is wakened in the early morning with a feeling of abdominal discomfort and distension. He then has an urgent call to stool and passes a large, soft, motion with much flatus. This relieves his discomfort and he may pass no more stools for the rest of the day. A few months later similar evacuations/

evacuations may take place in the forenoon. The patient's attention will be drawn to the character of the motions, which become increasingly paler and very frothy. Soon after the diarrhoea has become established the mouth symptoms commence.

Not every case of sprue, however, starts with diarrhoea. There are cases where the tongue and mouth symptoms have existed for months before any sign of diarrhoea.

In rare cases anaemia and loss of weight may precede the diarrhoea by several months. These cases without other symptoms are very difficult to diagnose at onset.

SYMPTOMS IN TYPICAL ESTABLISHED CASE.GENERAL.

The patient looks ill. His expression is anxious and worried. His countenance has a dusky palor and his skin seems transparent. A brownish-grey pigmentation over the malar prominences, forehead and cheeks is sometimes seen. He is easily tired and complains that exercise does not seem to do him good as formerly. He is often hungry, but is afraid to eat indiscriminately, as he known from experience that this will make his diarrhoea worse. He becomes very introspective, taking a great interest in his motions and becoming very depressed when the number of them is increased.

The cardio vascular system is normal, but the blood pressure is usually low.

The respiratory system has no symptoms of its own although broncho pneumonia may appear as a terminal symptom.

Muscular system. Troublesome cramps and carpo-pedal spasms may give the patient many a sleepless night. This is looked upon by some as a most unpropitious sign.

Nervous system. Tingling and numbness of the limbs are late symptoms and may be the forerunners of those/

those of combined degeneration of the cord, which will be dealt with in sequelae. The temperature, as a rule is normal throughout, though in the last few months of life it may be irregular. The occurrence of pyrexia must be regarded as being of a serious prognostic significance.

LOCAL SYMPTOMS.

Mouth. At first there appears a tenderness at the tip of the tongue, with the formation of little blisters, or apthae, on the fraenum, the buccal mucosa and inside the lower lip. The apthae are remarkably evanescent, as is also the inflammation of the tongue itself. This inflammation is of a peculiar kind and affects the fungiform papillae at the tip and the margins.

The mouth symptoms may subside as quickly as they commenced, but result in gradual atrophy of the filiform papillae, leaving the fungiform papillae standing out as angry inflamed knobs. This peculiar inflammation of the tongue may commence round an aptha and spread along the margins; at the same time the patient suffers from excessive salivation and disturbance of the sense of taste. He is extraordinarily sensitive to acid fruits, salts, hot drinks, curries and spices of all kinds. As the disease progresses, /

progresses, even light wine may cause the most intense pain and burning in the mouth. A curious point is that any exacerbation of mouth symptoms, in some patients, appears to be relieved by a recurrence of the diarrhoea, while again, in others, the exacerbations of the mouth and bowel symptoms coincide. As the disease progresses superficial longitudinal and transverse fissures make their appearance, but do not extend into the muscular tissue. The mucus surface of the tongue has now a highly polished appearance divided into a number of incomplete compartments by the fissures already mentioned. The buccal mucous membrane also becomes smooth and atrophic. The lymphoid tissue of the hard palate and the follicles on the mucus surface of the lower lip stand out prominently. Cracks and fissures may appear at the angles of the mouth and become extremely painful. Eventually, at the stage preceding death the whole tongue and mouth become covered with a grey growth of thrush fungus.

In the stomach acid dyspepsia and flatulence are constant symptoms. In the early stages the gastric juice may be normal or there may be hyperchlorhydria. In the later stages hypochlorhydria or achlorhydria is usually found. Vomiting is common, especially after indiscretions of diet. Abdominal pain is frequently complained of, especially just before the bowels /

bowels move. Meteorism is often extreme. The abdomen is distended, especially in the lower half and peristalsis may be observed to take place through the attenuated abdominal wall. Most clinicians place reliance, as an aid to diagnosis, on the shrinkage of the liver dulness, indicating a considerable degree of atrophy. Movement of the bowels may cause the patient great pain on account of the scalding feeling caused by the acid motions on the raw mucous membrane of the anus. Sometimes the motions are almost pure white but they are usually grey or light yellow. The usual consistence is that of porridge and the appearance is frothy. They have a characteristic sour odour. At times the motions are watery and again the patient may be constipated.

The general health of the patient eventually shows signs of giving way. He becomes extremely emaciated, dull and listless. The smallest action requires an effort. Any indulgence in diet or physical fatigue causes a recurrence of symptoms every time in a more acute form. With the gradually increasing weakness and emaciation the patient assumes the appearance of a most marked anaemia. The lips are pale and the eyes sunken. The ankles become oedematous and the skin dry and scaly. Pruritus ani and, in women, vulvi/

vulvi sometimes appears to add to the suffering. Emaciation becomes so extreme that the victim resembles a living skeleton. The diarrhoea becomes continuous and the patient takes to bed. If the anaemia is severe petechiae may appear on the extremities and buttocks. Less and less food is taken, so that death may supervene from inanition. In other cases a fatal termination may follow an acute choleraic attack, or may be due to some intercurrent disease.

Such is the story of an untreated case or of one which has not been recognised in the early stages, when treatment is of most avail.

Death may occur in a year from the onset of symptoms, while in a more chronic form the course of the illness may last as long as 20 years. In the latter group the mouth and bowel symptoms may be absent for long periods at a time.

Initial symptoms have been known to develop after a patient has left the tropics. In a case such as this, the disease must have been present in a latent form and been brought out by some factor, which lowered the patient's resistance.

Nicholls²⁸ (1918) describes a condition, common to natives of Ceylon, where the mouth and oesophagus closely resemble sprue in the European. These natives seldom complain of diarrhoea and the frothy stool, usual with Europeans, is absent. Nicholls concludes that/

that these are sprue and owing to racial immunity, the symptoms are much milder than in Europeans. A similar condition is described by Manson Bahr occurring amongst native prisoners in jails in Ceylon.

Occasionally dyspeptic symptoms may dominate the clinical picture.

The existence of the varied clinical forms seems to suggest that the morbid process has attacked different organs or parts of the intestinal canal.

The mouth symptoms and wasting may progress in the absence of diarrhoea. A case is occasionally met with, in which the diarrhoea subsides, yet copious solid stools continue to be passed and emaciation is progressive.

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COMPLICATIONS AND SEQUELAE.Ulceration and perforation of small intestine.

This is rare and when it does happen it is usually in the rapidly progressive type of the disease. It invariably terminates fatally.

Appendicitis.

Appendicitis may occur at any stage of the illness. In the early stage there is little risk from operation, but in the later stages the risk is great on account of the attenuated and friable state of the intestine and the poor resistance of the patient.

Sepsis.

Boils and local abscesses may occur especially round the anus and rectum.

Fissure in the Anus is sometimes the cause of considerable pain on defaecation.

Pneumonia.

When this occurs in late cases it is usually fatal.

Subacute Combined Degeneration of Cord.

Nervous changes are not common in sprue but several cases showing symptoms of subacute combined degeneration of the cord have been reported, Reed and Wyckoff/



Wyckoff¹¹ (1926), Wood¹³ (1925). The writer has also seen a case which is reported at the end of this section. The symptoms commence with numbness and tingling in the legs. This is followed by weakness, incoordination, spasticity and increased reflexes. Babinski's sign is positive. The next stage is marked by rapidly developing spastic paraplegia. The patient is unable to stand and rigidity may be extreme. Anaesthesia commences in both legs and ascends rapidly, loss of pain preceding touch. Lightning pains may occur in the legs. The stage of flaccid paraplegia, as far as records go, is never reached in sprue as the patient dies before these symptoms have time to develop.

The following three cases of the writer's are described in detail as being examples of a mild, an average and a severe case. Other cases are described in tabular form. All the cases mentioned were Europeans.

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CASE HISTORIES.

CASE 1. EARLY MILD.

Male 38. American Missionary. 5 years residence in South China, born and lived in California before going to China.

Personal History. No previous illness of note. Present illness began with diarrhoea. For 1 year prior to this he had had occasional loose, normal coloured stools in the morning. These loose stools occurred at intervals of 2-3 months at the commencement, their frequency increasing, till at the end of one year there were two loose motions every morning on rising. No complaint of sore mouth or tongue. Flatulence, dyspepsia and loss of energy combined to make him seek medical advice. Loss of weight, 10 lbs in last year.

Complaint. Looseness of bowels, loss of weight, mental depression, loss of energy.

Examination. Well built man, somewhat flabby. Skin rather yellowish; mucous membranes not anaemic; tongue and mouth normal; heart and lungs healthy; pulse 72, regular, easily compressible; Blood pressure systolic 110; diastolic 80; slight distension of lower half of abdomen, tympanitic to percussion; liver dullness normal; spleen not enlarged; sigmoidoscopy, no ulcers or anything to note; central nervous system/

system normal; test meal, Free HCl increased; urine acid S.G. 1016 no albumin, no sugar; stools bulky, dark brown, semi solid, containing mucus, no froth, foul odour, microscopically no amoeba nor ova, no Shiga or Flexner group organisms, Fat content of dried faeces 30%, no occult blood, bile pigments present. Blood: red corpuscles 4,300,000; haemoglobin 80, colour index .9; white corpuscles 7200; polymorphs 64%; lymphocytes 30% large mononuclears 3%; no parasites. Calcium content: ionic calcium 8.2 mg. per 100 cc., combined calcium 2.7 mg., total calcium 9.9 mg. per 100 cc.

Course and treatment. Rest in bed, milk diet, calcium grs XX t.i.d. and parathyroid ext. gr $\frac{1}{10}$ t.i.d. Two weeks later stools normal, diet increased but avoiding excess of carbohydrates and fat. Calcium stopped after 3 weeks. Parathyroid after 6 weeks.

Six weeks later gained 6 lbs., bowels normal, full of energy, cheery. Red blood corpuscles 4,800,000, haemoglobin 90%, white blood corpuscles 7900, calcium content: ionic calcium 10.5, combined calcium 0, total calcium 10.5 mg. per 100 cc.

Two years after treatment patient was perfectly healthy and had not suffered from another attack although remaining in the tropics. He continued to drink 2 glasses of milk a day.

This is a typical, early, mild case. It will be noted that the mouth and tongue were normal as was the colour/

colour of the motions. Anaemia was very slight and colour index under 1. The reduction of ionic calcium in the blood is an important point which is of considerable value in early diagnosis.

CASE 2.

Male 64. European, born in England. Lived at sea for 30 years, travelled all over world, lived in Hong Kong for last 15 years.

Personal History. Dysentery 30 years ago; several attacks of malaria, none in last 10 years; typhoid 20 years ago. Diarrhoea started 10 years ago; for first year colour of motions normal, after that became pale, almost white; mouth and tongue became sore 2 years after commencement of symptoms; long remissions sometimes as long as 2 years between attacks. Had been treated with emetine, with temporary improvement, santonin with temporary improvement, liver soup and sour milk, temporary improvement. Was sent to England for 1 year's holiday, but got worse there and returned to Hong Kong. Next put on calcium and parathyroid, improved rapidly but recurrence 2 years afterwards. This time calcium and parathyroid not so useful/

useful, diarrhoea recurred more often. Went to British Columbia to try strawberry treatment. Ate strawberries and cream for 2 months, no medicine. Great improvement, put on 20 lbs. Returned to Hong Kong. Symptoms again appeared nine months after and went on for 6 months. By this time he had all the classical symptoms of sprue, pale frothy stools, nausea, vomiting, sore mouth and tongue, dusky pallor and mental depression.

Examination. Thin, had evidently lost weight, mucous membranes pale; tongue glazed and cracked, papillae enlarged; heart feeble and slightly enlarged to left, pulse weak, blood pressure 108 systolic 80 diastolic; lower half of abdomen distended, tympanites, liver dulness diminished, one finger's breadth above costal margin in mammary line; spleen not enlarged; central nervous system normal; Wassermann reaction normal; urine 1012, acid no albumen or sugar; weight 120 lbs; stools, pale, bulky, frothy, test for bile pigments negative, no occult blood, fat content 45% of dried faeces; no ova or parasites present. Test meal, free HCl diminished.

Blood: reds 2,200,000, haemoglobin 50%; colour index 1.1; leucocytes 4000, polymorphonuclears 57%; lymphocytes 41%; large mononuclears 1%; eosinophils 1%; anisocytosis, poikilocytosis; calcium content, ionic Ca 6.9, combined Ca 2.8, total Ca 9.7 mg. per 100 cc.

Course/

Course and treatment. Rest in bed, milk, raw liver, 150 mg. per day. 1 week later weight 121 lbs, red cells 2,800,000, haemoglobin 55%. Liver caused vomiting so given liver extract and pancreatic extract. 2 weeks later weight 125 lbs, red cells 3,200,000, haemoglobin 60%. Diet increased, eggs, broth, toast. 6 weeks later weight 135 lbs, red cells 4,000,000, haemoglobin 80%. Made good recovery and has carried on his work for 2 years. One slight recurrence cleared up in 2 days on taking pancreatic and liver extracts. The ionic calcium in the blood rose at the end of 6 weeks to 10.4 mg. per 100 cc. with no combined calcium.

An interesting point in this case is the rise of ionic blood calcium which occurred without giving calcium and parathyroid medication. It also appears that there must have been liver and pancreatic deficiencies on account of the benefit derived from these extracts.

CASE 3. SEVERE.

Female 51. European. Lived in Hong Kong all her life with the exception of 5 years in Australia; married, 3 children.

Personal history. No previous illness to note. Present illness commenced with diarrhoea 8 years ago. At that time weighed 180 lbs. Treated by many doctors and all the known remedies but attacks of diarrhoea still recurred and now almost incessant. Diarrhoea mostly of watery type, very scalding on defaecation. Had to give up work and take to bed. Troubled with cramps and pains in legs.

Examination. Emaciated and extremely pale, skin earthy tint and hanging in folds, petechiae on back of hands, forearms, buttocks. Weight 100 lbs. Tongue clean, glazed, prominent papillae, fissures; teeth bad; heart normal, pulse very feeble; blood pressure systolic 90, diastolic 60; abdomen, wall thin and flaccid; subcutaneous fat absent; liver dulness diminished to 4 inches on right mammary line; test meal, achlorhydria; urine, acid, 1008, faint trace albumen, no sugar; stool, no ova or parasites, pale, watery, mucus present, sometimes a little blood, frothy; test for bile pigments negative, fat content 40%.

Blood. 950,000 reds, haemoglobin 30%, colour index 1.6; leucocytes 2000; polymorphs 42%; lymphocytes 56%; large/

large mononuclears 1%; eosinophils 1%; anisocytosis, poikilocytosis and nucleated reds; Calcium content ionic Ca 4.9, combined Ca 4, total Ca 8.9 mg. per 100 cc.

Nervous system. Weakness and inco_ordination in legs, spasticity and increased reflexes. Babinski's sign positive.

Course and treatment.

Different treatments tried, calcium and parathyroid, liver and pancreas extracts, streptococcal vaccines, none of any avail. Gradually got worse, complained of tingling and numbness and lightning pains in legs. Developed spastic paraplegia, unable to stand. Pain left legs and slowly ascending anaesthesia developed. Weight dropped to 70 lbs, incessant vomiting and diarrhoea. Patient died from inanition.

Interesting points in this case are the serious degree of anaemia with nucleated reds, which are rarely seen except in very severe cases. When seen they are of serious prognostic significance. The complication of combined degeneration of the cord is of interest, on account of its association with pernicious anaemia. The calcium content of the blood is abnormally low.

TABLE OF MORE IMPORTANT SYMPTOMS IN 7 CASES.

Case.	4	5	6	7	8	9	10
	male	female	female	male	male	female	male
Age.	31	28	49	50	54	47	55
Residence in tropics.	4 years	28 years	15 years	22	25	18	10
Duration of illness.	4 months	8 months	1 year.	2 years	2½ years	3 years	5 years.
Initial symptom.	diarrhoea	diarrhoea	diarrhoea	diarrhoea	diarrhoea	diarrhoea	diarrhoea
Loss of weight.	5 lbs.	8 lbs.	12 lbs.	28 lbs	24 lbs.	38 lbs.	35 lbs.
Free HCl.	increased	increased	normal	normal	reduced	reduced	normal
Stools:-							
bile pigment	present	present	absent	absent	present	absent	absent
Fat content.	25%	30%	35%	45%	34%	41%	46%
Blood:-							
red cells	5 million	4,800,000	4,500,000	3,800,000	4,000,000	3,200,000	2,600,000
haemoglobin	100%	90%	85%	80%	80%	75%	70%
white cells	8000	7600	7800	7000	8000	4500	5000
ionic calcium mg. per 100 cc.	9.	8.6	8.	7.	8.1	6.2	6.4

These cases are arranged in order of the duration of illness. It will be noted that in the early cases, free HCl in the stomach tends to be increased, loss of bile pigment with pale motions is not a feature, anaemia if any is very slight and of the secondary type, ionic blood calcium is reduced in proportion to severity of disease.

In the later cases it is to be noted that free HCl tends to be diminished, bile pigment absent with increase in fat content of stools, the anaemia is of the pernicious type. Here again the ionic blood calcium gives a good indication of the severity of the disease.

DIAGNOSIS AND TREATMENT.

The diagnosis of sprue, as early as possible, is of the greatest importance. The disease, at the beginning, yields much more readily to treatment and the earlier treatment is commenced, the better the prognosis. The onset being so insidious, the early diagnosis presents a certain amount of difficulty. The only initial symptom may be a slight looseness of the bowels for a few days and the motions have no characteristic appearance. A feeling of lassitude may persist after the diarrhoea has ceased. A patient, having complained of such symptoms, should be kept under careful observation. The stools should be thoroughly examined for amoebic and bacillary dysentery and ova of intestinal parasites. A note should be made of the patient's weight. Next time the patient complains of looseness of the bowels another examination of the stools should be made. If this is negative the ionic calcium content of the blood should be ascertained. Any reduction of the ionic calcium content of the blood associated with loss of weight and diarrhoea should be considered an indication of sprue. If there is any doubt at this stage, it is far better to treat the case as sprue than to wait for some classical symptom to develop.

There/

There are three prominent symptoms, which occur in other diseases from which sprue must be distinguished, namely diarrhoea, sore mouth and anaemia. The diarrhoea is to be distinguished from hill diarrhoea, chronic amoebic or bacillary dysentery and chronic pancreatitis.

Hill diarrhoea occurs commonly in the hill stations of India at an elevation of 6000 ft. or over. It attacks new comers and is apt to occur in epidemics and at certain seasons of the year. Like sprue it is characterised by a flatulent dyspepsia, by nausea and by the passage of large, liquid, pale fermenting stools and the tendency of the diarrhoea to occur in the early morning. There are, however, no mouth symptoms. Sometimes diarrhoea may persist for a considerable time and may develop into or predispose to genuine sprue. Rainy

There is little danger of confusing a chronic amoebic or bacillary dysentery with a case of sprue. In amoebiasis the main points in differential diagnosis will be the history of intermittent passage of blood and mucus, the presence of pain over various portions of the intestinal canal, as for instance over the transverse colon, the character of the stools, the presence in them of *entamoeba histolytica* or its cysts. In the case of bacillary dysentery, the characteristic/

characteristic cellular exudate in the stools and serum agglutination tests will determine the diagnosis. Very early sprue, before the mouth symptoms develop and hill diarrhoea might be confused. In this case the ionic calcium content of the blood would give a valuable clue. Scott²⁹ gives the calcium content of the blood in 105 cases other than sprue, i.e. diarrhoea, amoebic and bacillary dysentery, mucous colitis and syphilis, malaria, kala-azar, filariasis, undulant fever etc. The ionic calcium averaged 10.2 mg. per 100 cc.

Pancreatitis in advanced cases presents a wonderful clinical likeness to sprue. There is the passage of large, bulky, colourless motions of acid reaction, with great, often rapid emaciation. Distension of the abdomen, anaemia and tongue symptoms may also be present. Pancreatitis is however rarely primary. It is often malignant and secondary to disease of the liver, gall bladder and ducts. Begg³⁰ believes that all chronic sprue cases have pancreatitis. Careful examination ought to distinguish the two diseases. In sprue the liver is diminished in size and in pancreatitis the head of the pancreas may be felt enlarged, with tenderness of pressure on the abdomen. Also in pancreatitis there is always a history of attacks of fever, while the tongue, if affected, will show only aphthous patches and sugar will/

will frequently be found in the urine.

The mouth symptoms must be distinguished from those of pellagra, syphilis, the inflammation caused by excessive smoking, pyorrhoea, or carious teeth.

Syphilis. The tertiary syphilitic tongue, in contra distinction to that of chronic sprue, shows large areas of leukoplakia; other syphilitic stigmata may also be present. The apthae might possibly be mistaken for the mucus patches of secondary syphilis. The Wassermann reaction would clear up any doubt.

Smoker's tongue. The inflammation involves the fungiform papillae where the smoke impinges on the tongue and there may also be superficial leukoplakia.

Pyorrhoea affects the gums at the alveolar margin and a carious tooth would only cause inflammation on one side.

Sprue must be distinguished from other diseases in which anaemia is a prominent symptom. Such are pellagra, ankylostomiasis, pernicious anaemia, chlorosis, chronic malaria, kala-azar and scurvy.

From pellagra sprue can be distinguished by the complete absence of cutaneous symptoms so characteristic of that disease. In pellagra there is often a general inflammation of the tongue and the passage of frothy and gaseous stools. The inflammation however is general and not confined to definite areas. The fat content/

content of the stools and ionic calcium content of the serum in sprue are also diagnostic features.

Ankylostomiasis is often associated with a chronic diarrhoea, but the absence of mouth symptoms, the eosinophilia and the presence of ova in the stools afford sufficient grounds for differentiation.

Chlorosis may be distinguished from sprue by the plump condition of the patient and the absence of diarrhoea.

Chronic malaria may be confused with sprue; but the splenomegaly together with a history of febrile attacks, the mononuclear increase and perhaps the presence of parasites in the blood, should serve as a guide.

In Kala-azar there is usually a great enlargement of the liver and spleen together with an intermittent pyrexia, all of which are not found in sprue.

The comparison of Pernicious Anaemia and sprue has been already gone into. The important points in sprue for differentiation are increased fat content of stools, absence of bile pigment from stools, diminished liver dulness, tetany, rapid wasting, mental depression and origin in tropics.

In scurvy there will generally be a history of diet deficient in vitamines; haemorrhages are common and the stools do not have the typical appearance of the sprue stool. In scurvy the anaemia is always of the secondary type.

P R O G N O S I S.

Much depends on how long the disease has been going on before it is recognised. The prognosis is as a rule favourable for cases, which have been carefully treated in the early stages of the disease, even if they continue residence in the endemic area. For patients over middle age with the disease well established, the prognosis depends to a great extent upon the locality in which they live. A warm dry, temperate climate seems to be most suitable. In such a climate the outlook is good. If these patients continue residence in the tropics the prognosis is not so favourable, as it is impossible to guarantee that they will not have a recurrence, even though apparently cured. The prognosis is worst for elderly patients, with the disease well established, who have led a hard active life and who are not in a position to leave the tropics. When once a man has suffered from sprue and has recovered, it is advisable that he should lead a well regulated existence for the rest of his life.

T R E A T M E N T.

Treatments of this disease are legion. The reason for this is that, in the early stages at any rate, it is a disease of remissions and treatments applied just before the remissions may be credited with the cure. Again the mere transference of the patient to a suitable climate, in many early cases, is sufficient to effect a cure. Such a patient, in his new locality, is possibly under a doctor unacquainted with the disease and the improvement is put down to the doctor's treatment. Cure of the disease in the endemic area is a very different thing to curing it in healthier regions. Many writers assert that for proper treatment it is essential that the patient be removed to a temperate climate. With modern methods of treatment this is no longer necessary in early cases. In well established cases it is still desirable. Transference from a hot to a cold climate should not be too sudden. If a weak patient is faced with a long sea journey, it is advisable to start treatment and get him as well as possible first, as the ordinary ship's diet, which is most unsuitable, may make him worse. It is rare to obtain an adequate supply of fresh milk, which is so essential, at sea. Cases, which might have been saved, have been known to die on the voyage home, as a result of the neglect of this elementary precaution.

Milk treatment. For patients who can take milk, there is no doubt that it is easily the best form of nourishment in this disease. The milk must be pure and fresh, procured from the best cows and rich in cream. It should not be boiled but if it comes from unreliable sources it may be sterilised by heating it to 140^oF.

The patient must be kept in bed in a bright room. A hot water bottle at the feet will often be found necessary, as, owing to the general debilitated condition and the anaemia, sprue patients suffer greatly from cold feet. A warm abdominal binder should also be used.

It is advisable to commence treatment with a dose of Castor Oil $\frac{1}{2}$ oz. The milk should not be gulped down, but sipped. It should be given in small amounts, but frequently. At the start, three pints in 24 hours is usually sufficient. At the commencement of treatment there may be a marked loss of appetite and it is not advisable to increase the amount of food till the desire for it is established, or till the motions have become solid.

The patient should not be allowed to get out of bed and must use the bed pan and urine bottle.

The patient's general condition improves after 3 or 4 days. This can be judged by the solid character of the stools, the amelioration of the dyspeptic symptoms /

symptoms and general mental outlook.

The quantity of milk may now be increased by the addition of half a pint daily till a maximum of 5 or 6 pints is reached.

Patients are apt to become extremely constipated on a milk diet. This may be corrected with liquid paraffin, or small doses of castor oil.

Dyspeptic symptoms, should they continue, may be relieved with bismuth and soda.

The progress of the patient under treatment is gauged by increase in weight, diminution in weight of stools and darkening of their colour; amelioration of tongue and mouth symptoms; persistence of appetite; lessening of anaemia as judged by red cell count and estimation of haemoglobin. A chart should be kept of the average daily weight of the stools. Sir Patrick Manson recommended that for six weeks from the time the stools become solid and the mouth free from irritation, no food or drink other than milk, should be added. After this may be added gradually raw eggs, small quantities of malted foods, calfs foot jellies, rusks and crisp toast. Carbohydrates should be added gradually on account of the carbohydrate intolerance which exists in sprue. At this stage the patient may be allowed to get up and take carefully graduated exercise out of doors. He must never be allowed to become fatigued. While the patient is in bed massage is/

is of benefit in restoring tone to the muscles and promoting assimilation. Should the patient continue his improvement the diet may be increased with fruit, pounded fish and chicken broth. Finally chicken and shredded meat may be introduced. Some authorities allow white wine or some mild stimulant: from the writer's experience he finds that alcohol is better avoided altogether. Smoking may be allowed after the mouth symptoms have disappeared.

The writer has found this form of diet excellent. In temperate climates it may effect a cure, but in the tropics it is not sufficient by itself to prevent relapses. Combined with other forms of treatment it is most useful.

Fruit treatment has been used much, especially by those who believe in the food deficiency theory of causation. Van der Burg was the first to suggest it.

Many patients do well on fruit from the commencement. It is better combined with milk and often does good where the strictly limited milk treatment may fail.

Strawberries have been most generally recommended. Thin first recognised the value of strawberries and since his time Manson and others have expressed their belief in the value of this fruit. The strawberries should/

should be fresh and, as with other diets, should be given sparingly at first; gradually increasing till 3 or 4 pounds are taken daily with milk.

Patients do seem to derive benefit from this treatment, but it is not a cure and strawberries are not as a rule obtainable in the tropics.

Fresh bananas crushed up with sugar and cream have been recommended. The writer has never found any benefit from this fruit and considers it too rich in carbohydrate.

Papaya agrees with most patients. It may be of distinct benefit especially in cases with dyspeptic symptoms, perhaps on account of containing papaine.

Bael Fruit has long been used by natives as a remedy for diarrhoea. This fruit was first brought to the notice of European practitioners in 1878. The medicinal properties seem to reside in tannic acid, an essential oil and a bitter principle. In Ceylon and India this fruit can be obtained at all seasons. The soft pulp is given raw with sugar and cream in gradually increased quantities.

The reputation which this fruit has attained is probably on account of its astringent action, which stops the diarrhoea. The use of astringents in sprue is not always desirable.

Cherries, prunes and pears have been recommended by Van Dooren³¹.

Begg³⁰ /

Begg³⁰ states that raspberries, cranberries, pumeloes and mangoes may all be used.

Elders³² recommends a mixed milk, fruit and meat diet.

Preserved, canned or dried fruits have not the same beneficial effect of fresh fruits.

The writer has found fresh fruit a valuable addition to sprue diets. Pineapples, oranges and grapes, however, he has found unsuitable.

Treatment with shredded meat and meat juices.

There are a few patients who cannot tolerate milk. These may do well on this treatment. At the commencement the juice of fresh lean meat is given with warm water. The meat may be either raw or underdone. As the patient progresses shredded steamed beef may be given, then under done minced meat. The amount is gradually increased up to 3 pounds per day. Warm water is drunk on going to bed and on rising in the morning, it should not be taken with meals.

When a patient gets very tired of milk, this diet is useful as an alternative for 2 or 3 days.

Santonin Treatment.

Begg³⁰ has advocated the use of this drug for many years. He uses old yellow santonin. This is obtained/

obtained by exposing white santonin to the rays of the sun for at least 6 months in sub-tropical regions. It is given in doses of gr. V twice daily. Each dose is well rubbed into one teaspoonful of olive or almond oil. He claims that the first noticeable result, of the good done by santonin, is the rapid enlargement of the liver. Within 24 hours of administering the first dose the size of the liver becomes normal. The drug may be given in courses of from one week to one month according to the progress of the patient. Begg claims that during his practice in the East he never had a failure with this remedy.

Other observers have not been able to convince themselves of any specific value of this drug.

The writer has treated three cases on the lines laid down by Begg. Each case was benefitted at the time, but all of them recurred within a year. One of these cases was an old sea captain. He had great faith in the remedy and used to expose his santonin to the sun on the bridge of his ship. On the first sign of a recurrence he would give himself a week's treatment which kept away the disease for several months. In the course of three years he had five recurrences.

Emetine has been recommended by Rogers¹⁴ in conjunction with streptococcal vaccines. Manson Bahr³ is/

is convinced that its use aggravates rather than ameliorates the symptoms. The writer has known of several cases of sprue which were diagnosed as chronic amoebic dysentery at the commencement. They were treated with emetine and in none of them was a beneficial result noted. It is possible that in some of the cases reported improved by its use there may have also been an amoebic infection.

Vaccine Treatment.

Rogers¹⁵ has treated 17 cases, over four years, with autogenous streptococcal vaccines. The patients treated by him included a number who were suffering from the disease in the advanced stages. In all cases improvement resulted and in the majority complete cures.

Nicolls⁷ treated nine cases with autogenous streptococcal vaccine with satisfactory results, giving doses of 100 million every five days.

Other observers have not reported such encouraging results with these vaccines. The writer treated one advanced case with autogenous streptococcal vaccine without noting improvement. He also tried anti-streptococcal serum with an equally disappointing result.

Monilia/

Monilia vaccines.

Ashford³³ (1925) reported his results with vaccines of *Monilia psilosis*. In order to subject the vaccine therapy to a severe test, he withheld all drugs and encouraged an excess of fats, cereals and sugar. Two of these cases were cured, the symptoms disappearing in 31 days. Three others were liberated of all evidence of sprue in 65 days, but did not gain weight. Of the remainder, four were improved and one died. Injections were given, as a rule once weekly, of a 1% sediment of killed culture of *Monilia psilosis*, suspended in a normal salt solution, in an ascending scale of dose from .1 - 1 cc. Eight injections were required as a rule. In a fair proportion of those inoculated there was noted on the second or third day weakness, increase of meteorism, diarrhoea and an exacerbation of sore tongue. Ashford states that while cures of sprue apparently occur from diet alone, prolonged observation seems to justify the employment of specific vaccines.

Manson Bahr³ reports that he has pursued this line of treatment but has not formed any favourable opinion as to its value.

The writer has had no experience with this vaccine. Ashford's results are not convincing and no great success in its use has been reported.

Batavia Powder.

Batavia Powder or powdered cuttle fish bone and crabs eyes has had a certain local reputation in the treatment of sprue. This proprietary concoction is also known as Sys' specific. Any value it may have probably comes from the calcium in the cuttle fish bone.

CALCIUM AND PARATHYROID TREATMENT.

The administration of calcium lactate and parathyroid extract in sprue, advocated by Scott,³⁴ has constituted a great advance in treatment. No other treatment has produced so many reports of success, in the hands of independent workers, as has this. Writers may assert that the treatment is not original but Scott was the first to bring it into prominence and investigate it thoroughly and by so doing has been responsible for the relief of much suffering.

Treatment consists of putting the patient to bed for the first 14 days and allowing milk only. At the beginning $3\frac{1}{2}$ - 4 pints daily are allowed, increasing by $\frac{1}{2}$ pint a day till 7 - $7\frac{1}{2}$ pints are reached. Calcium lactate is given in cachets, containing gr XV each, thrice daily and parathyroid extract gr $\frac{1}{10}$ twice daily. It is absolutely essential that the extract should be free from thyroid. Constipation should be corrected with liquid paraffin. Plain biscuits may be allowed from the tenth day onwards, by which time the ionic calcium has increased to between 7 and 8 mg. per cent. At the end of 3 weeks the average patient can take milk puddings, eggs, fish, potato, carrot and bananas; and in the fourth week chicken and fruits. The calcium can be reduced in the 3rd - 4th week and stopped at the end of the fourth. The parathyroid extract/

extract should be continued in full doses till the fifth week, then reduced until it is stopped altogether at the end of six weeks. This, however, can only be gauged with certainty by the blood test.

Favourable reports on this treatment have been recorded from most of the endemic centres of sprue in various parts of the world.

It is not claimed by Scott as a certain specific as some cases he reports were only improved, some recurred and two died of anaemia.

The writer has used this treatment since it was first advocated by Scott in 1923. He has found it of very marked benefit in the early cases and, in these, uses it as a routine. In later cases the results are not so certain. He had one case which recurred yearly for 3 years in spite of calcium and parathyroid treatment. This case eventually did well on treatment with liver and pancreatic extracts.

Out of 25 cases treated by the writer with parathyroid and calcium, 13 recovered and showed no symptoms 2-3 years afterwards. 11 recurred and one died.

TREATMENT WITH LIVER AND LIVER AND PANCREATIC EXTRACTS.

For many years liver soup has been popular in the diet of sprue patients. This popularity has stood the test of time and liver soup is still largely used. The biliary functions of the liver are deranged in sprue and some light was thrown on this subject by an investigation upon the cholesterol output in the faeces, reported by Newham²⁶ (1926). The cholesterol introduced into the bowel, with the bile, is excreted in the faeces as stercorin, but in no case of sprue did the output approach the normal. The output of stercorin varied from 0.147 to 0.328 gm. in 24 hours.

The cholesterol content of the blood is also lowered for in eleven cases of sprue, investigated by Newham and Morris¹², there was a definite hypocholesteraemia.

Van Steens²⁵ (1926) found in samples, taken from the duodenum by the duodenal tube, that the constituents of the bile were below normal in 3 cases of sprue.

It has been observed by Lewis³⁵ that the digestive disturbances peculiar to sprue can be greatly improved by the administration of bile salts. Begg³⁰ also states that ox gall has proved useful in certain cases.

In 1925 the writer decided to try the effect of treatment/

treatment with raw liver. Six cases were treated and the results are shown in the following reports.

Four cases were apparently cured and two cases required further treatment with pancreatic extract.

In sprue, as well as the derangement in biliary function, there is also a pancreatic insufficiency. Ashford³³ recorded that in a number of examinations of duodenal secretion, recovered by the Einhorn tube from undoubted cases of sprue, half revealed no lipase while the other half showed a well marked insufficiency.

Silverman and Denis²⁷ in an investigation of the duodenal contents found that the lipolytic, amyolytic and proteolytic activities were very much diminished.

Brown³⁶ (1921) states that in an examination of the duodenal contents extracted by Einhorn's bucket in 5 cases, no pancreatic ferments were found. He mentions that all were treated by pancreatic extract and much improved, but symptoms reappeared when treatment was stopped.

Lambert³⁷ (1923) reports that he contracted sprue in Queensland and treated himself with dilute HCl M XV and Pancreatin gr X t.i.d. He was cured and able to remain in the endemic centre. This treatment was much used along the Queensland coast.

It/

It occurred to the writer that his cases which did not progress satisfactorily with raw liver, might be benefitted by the addition of pancreatic extract. The only extract he could obtain was a French proprietary preparation called "Pancrepatine". This consists of extract of liver and extract of pancreas in keratin coated capsules. Six cases were treated with encouraging results. Another case died. This case was reported in section 5 as case 3. The patient was extremely emaciated before treatment was started. The usual milk treatment was carried on at the same time with the addition of meat, fish, fruit and toast as the patients progressed.

Each patient was given as much of these extracts as he could tolerate, an overdose being indicated by a feeling of nausea one to two hours afterwards. The capsules containing the extracts were given before food, four capsules three times a day being the usual dose.

The following reports of cases show the results obtained.

CASE 1.

Male 31. Residence in Far East 5 yrs, Shanghai 2 yrs, Hong Kong 3 yrs.

Had suffered from diarrhoea for 2 years, three or four motions daily mostly in morning. Motions were white, semi solid and frothy. Mouth had become sore during last year. Complained of dyspepsia and acidity. Normal weight 170 lbs had dropped to 146 lbs. Test meal, hyper-chlorhydria present.

	<u>Before treatment</u>	<u>After 2 weeks</u>	<u>After 2 months.</u>
Weight in lbs	146	157	166
Blood:-			
red cells	4,000,000	4,300,000	5,000,000
haemoglobin	80%	85%	95%
ionic calcium mg. per 100 cc.	7.1	7.8	10.4
Stool:-			
fat content dried	39%	34%	30%

Above table shows effect of raw liver treatment 6 oz per day for 8 weeks combined with milk treatment. Eggs, fish, meat and toast were added as patient improved.

Two years later patient was free from symptoms and had had no recurrence.

CASE 2.

Male 42. Residence in tropics 14 years.
History of dysentery 5 years ago. Usual weight
160 lbs.

Diarrhoea started 1 year ago with loose pale
yellow, bulky motions. Tongue very sore, red and
glazed. Test meal, Free HCl normal.

	Before treat- ment with <u>raw liver.</u>	After <u>2 weeks.</u>	After <u>8 weeks.</u>
Weight.	140 lbs	148 lbs.	160 lbs.
Blood:-			
red cells	3,100,000	3,900,000	4,500,000
haemoglobin	70%	80%	90%
ionic calcium	6.8	8.0	10.8
Stool:-			
fat content dried	40%	35%	28%

Table shows effect of raw liver treatment 6 oz
per day with milk; eggs, meat, fruit and rusks added
after first 2 weeks. Patient reported well $2\frac{1}{2}$ yrs
after treatment.

CASE 3.

Female 56. Residence in China 11 years.

Nine years ago she was thought to be suffering from dysentery and treated with emetine. Shortly after this, motions became pale coloured, later on mouth became sore. Treated with calcium and parathyroid 2 yrs ago, much improved but recurred 1 yr ago.

Again treated with calcium - parathyroid but recurred 2 months ago. 10 yrs ago weighed 130 lbs.

Test meal normal Free HCl.

	Before treatment with raw and dried liver.	After 2 weeks.	After 12 weeks.
Weight in lbs	79	85	110
Blood:-			
reds	1,000,000	2,400,000	4,000,000
haemoglobin	30%	60%	80%
ionic calcium mg. per 100 cc serum.	6.0	7.8	10.0
Stool:-			
fat content dried	40%	37%	32%

This patient was treated with raw liver 6 oz per day for 1 week. She objected strongly to taking it so was given dried liver 4 oz per day for 11 weeks. Milk was given for first week, eggs and meat juice added during 2nd week, and fish, chicken and fruit after 3 weeks. She left for America after 12 weeks treatment but reported by letter 2 years later to say that she was in the best of health and weighed 125 lbs.

CASE 4.

Male 54. Residence in tropics 25 yrs. History of malaria and operation for appendicitis. Diarrhoea started $2\frac{1}{2}$ yrs ago. Motions not very pale coloured. Had been treated with santonin also calcium and parathyroid. Both remedies caused improvement but did not prevent recurrence. Normal weight 154 lbs. Test meal hypochlorhydria.

	Before treatment with dried liver.	After 2 weeks	After 8 weeks.
Weight in lbs	130	140	155
Blood:-			
red cells	4,000,000	4,300,000	5,000,000
haemoglobin	80%	90%	100%
ionic calcium mg. per 100 cc serum.	8.1	9.	11.
Stool:-			
fat content dried	34%	30%	28%

Dried liver 4 oz per day was given for 6 weeks. Milk only given for first week followed by meat juice, eggs, fruit, toast. Full diet in 3 weeks.

2 years after treatment patient in excellent health, weight heavier than normal - 160 lbs.

CASE 5.

Male 64. Life at sea followed by 15 yrs residence in Hong Kong. History of malaria, typhoid and dysentery. Diarrhoea started 10 yrs ago. Mouth and tongue symptoms commenced 2 yrs after diarrhoea. Had been treated with emetine, santonin, liver soup, strawberries, calcium and parathyroid. Weight before illness 170 lbs. Test meal, hypochlorhydria present.

	<u>Before treatment</u>	<u>After 1 wk. treatment with raw liver.</u>	<u>After 2 wks treatment with liver & pancreatic extracts.</u>	<u>After 6 wks. treatment.</u>
Weight	120	121	125	135
Blood:-				
red cells	2,200,000	2,800,000	3,200,000	4,000,000
haemoglobin	50%	55%	60%	80%
ionic calcium.	6.9	-	-	10.4
Stool:-				
fat content dried.	45%	-	-	29%

Treated for 1 week with raw liver, anaemia improved but diarrhoea and sore mouth remained, liver caused vomiting. Changed on to pancreatic and liver extracts, immediate improvement. Milk given for 2 weeks followed by meat juice, eggs, fish and fruit. 2 yrs later patient in excellent health, weight 160 lbs; had one slight recurrence which cleared up in two days on taking pancreatic and liver extract.

CASE 6.

Male 28. Residence in tropics 8 years.

History of pneumonia 3 yrs ago. Led very strenuous outdoor life, often travelled in interior of China for weeks. Diarrhoea started 6 months ago, motions had been pale coloured but formed for the previous 3 months. Sore mouth started 2 months after diarrhoea. Normal weight was 156 lbs. Test meal, hypochlorhydria present. Had been treated with calcium and parathyroid for 6 weeks with temporary improvement of diarrhoea but no gain in weight.

	<u>Before treatment</u>	<u>After 2 weeks raw liver.</u>	<u>After 2 wks. ext. of liver and pancreas.</u>	<u>After 8 wks. ext. of liver and pancreas.</u>
Weight.	126	126 lbs.	134	150
Blood:-				
red cells	3,300,000	3,800,000	4,200,000	4,800,000
haemoglobin	75%	80%	85%	95%
ionic calcium	6.8	7.	8.5	10.4
Stool:-				
fat content dried.	50%	50%	38%	30%

The above table shows that raw liver treatment caused improvement in anaemia, but no increase in weight or diminution of fat content of stool. When liver and pancreatic extracts were given immediate all/

all round improvement occurred. The high fat content of the faeces will be noted pointing to greater derangement of pancreatic function.

Patient had had no recurrence 20 months after finishing treatment and was in good health.

CASE 7.

Female, 49. 12 yrs residence in Far East, Singapore, Shanghai and Hong Kong. Diarrhoea with pale motions first started 7 years ago. Had been treated with emetine, santonin, sour milk, autogenous vaccines, calcium and parathyroid. Weight before illness had been 120 lbs. Test meal, Free HCl absent.

	<u>Before treatment</u>	<u>After 2 wks pancreatic and liver extracts.</u>	<u>After 8 weeks.</u>
Weight in lbs	85	92	112 lbs
Blood:-			
red cells	2,100,000	2,500,000	4,100,000
haemoglobin	50%	60%	80%
ionic calc ^m .	7.2	8.1	10.2
Stool:-			
fat content dried.	48%	38%	32%

This patient on account of the high fat content of the stool, was put straight on to pancreatic and liver extracts. Milk meat, fish and fruit as usual were given. 6 months after treatment patient was well and left the Far East. No further information was received from her.

CASE 8.

Male, 47. Eurasian. Born and lived all his life in the Far East. History of dysentery 7 years ago. Pale loose motions for 1 year. Only treatment received was from Chinese doctor with Batavia Powder. This stopped diarrhoea but gave him "pains in stomach". Mouth just become sore. Normal weight not known but has got thinner. Test meal, normal Free HCl.

	<u>Before treatment.</u>	<u>After 2 wks pancreatic and liver extracts.</u>	<u>After 8 weeks.</u>
Weight in lbs.	160	169	182
Blood:-			
red cells	3,500,000	3,900,000	4,700,000
haemoglobin	60%	75%	95%
ionic calc ^m .	-	-	-
Stool:-			
fat content dried.	49%	-	33%

Two years after treatment patient was in good health. He was fond of very rich food and consumed a fair amount of alcohol. In spite of this he had had no recurrence.

CASE 9.

Male, 51. Residence in China 24 years.
 Had suffered from indigestion for many years.
 Disease started acutely 3 years ago with diarrhoea
 and sore mouth. Was sent home to England where he
 was treated with calcium and parathyroid. Diarrhoea
 and sore mouth disappeared but anaemia remained.
 Returned to China one year ago, symptoms reappeared
 9 months later. Weight before illness 172 lbs.
 Test meal, free HCl absent.

	<u>Before treatment.</u>	<u>After 2 wks pancreatic and liver extracts.</u>	<u>After 10 weeks.</u>
Weight in lbs	140	147	160
Blood:-			
red cells	1,500,000	2,000,000	4,000,000
haemoglobin	45%	50%	80%
ionic calcium.	6.8	8.	10.1
Stool:-			
fat content dried.	48%	40%	27%

Treatment combined with diet of milk, fruit,
 fish and toast. Patient reported 17 months after in
 excellent health. Weight 170 lbs.

CASE 10.

Male, 37. Residence in Hong Kong 6 years. Had had one loose motion a day for last 2 years. Motions normal colour, caused no inconvenience. In last two months motions had become almost white and more numerous and the tongue had become sore at the edges. Normal weight 190 lbs. Test meal, Free HCl normal.

	<u>Before treatment.</u>	<u>After 2 wks. pancreatic and liver extracts.</u>	<u>After 8 weeks.</u>
Weight in lbs.	180	185	190
Blood:-			
red cells	4,500,000	4,800,000	5,000,000
haemoglobin	90%	95%	100%
ionic calcium	9.	9.8	11.1
Stool:-			
fat content dried.	47%	35%	29%

Treatment with liver and pancreatic extracts was only carried on for 1 month as patient was so much improved. $2\frac{1}{4}$ years after treatment there had been no recurrence and motions were normal.

From these results it appears that in some cases the pancreas is affected more than in others as evidenced by the improvement produced by pancreatic extract. In these cases it will be noted that the fat content of the stools is abnormally high.

In cases where the pancreas is less affected as indicated by the lower fat content of the stools, liver treatment alone would seem to suffice.

It may be that the invasion of the pancreas by some micro-organism causes the insufficiency of secretion; perhaps the derangement of biliary function is responsible; or possibly over-stimulation of the pancreas in the early stages may result in a later loss of function. The foregoing records of cases tend to show that in the early cases free HCl in the stomach is increased while in the later cases it is diminished. This may have some influence on the pancreatic secretion.

That the pancreas is not permanently damaged is demonstrated by the fact that it regains its lost functions.

The writer regrets that he has not been able to investigate the pancreatic functions, in his cases, by means of the duodenal tube, but all of them were seen in private practice, also there were no facilities for such investigations in Hong Kong.

This/

This treatment is not claimed to be anything more than symptomatic, but it may tide the patient over a critical period and allow the liver and pancreas to regain their lost functions. One marked result is the effect of liver or liver extract on the anaemia. This is of interest on account of the recent advances made in the treatment of pernicious anaemia with raw liver, first reported by Minot and Murphy³⁸ in 1927.

TREATMENT OF SPECIAL SYMPTOMS.

Mouth and Tongue. The mouth should be kept in as clean a state as possible. A hard tooth brush should not be used as this tends to increase the inflammation of the gums. The mouth should be washed out with some mild antiseptic; glycerin and borax or glycothymol have proved useful. Aphthæ may be treated by the application of a silver nitrate stick to the abraded surface.

Lack of Assimilation. Patients who cannot tolerate three or four pints of milk a day and whose symptoms are aggravated by any further increase in the diet, will sometimes take feeds obtained by slowly evaporating the milk in a vessel surrounded by a jacket of hot water so as to reduce its bulk without diminishing the solids.

Nutrient enemata are sometimes used in cases with severe vomiting or with liquid stools containing undigested remains. These enemata may consist of peptonised milk or meat extracts and should be given in 6 oz doses every 4 - 6 hours. The rectum should be washed out before the enema.

For Pruritis and excoriation of the anus ichthyol ointment has proved of use. If pain or irritation is extreme a cocaine suppository may be used, /

used, but this is apt to increase the irritation when the effect of the suppository has worn off.

Persistent dyspepsia is best treated by reducing the amount of food given at each meal and by decreasing the intervals between them. Bicarbonate of soda in hot water often alleviates the condition. There are some practitioners who use alkaline mixtures throughout the whole course of the disease as they believe that the growth of yeasts in the intestinal canal is inhibited by the presence of alkalis.

Diarrhoea. If this is severe m^{XV} of tincture of opium gives great relief, but this should not be used as a routine. The diarrhoea usually ceases soon after the patient is put on an exclusively milk diet.

Constipation. Frequently, on the cessation of diarrhoea, a most obstinate constipation supervenes. If this is not relieved abdominal distension becomes very distressing. This is best treated with soap and water enemata, the bowels being kept regular with liquid paraffin.

Anaemia. This has been treated in the past with injections of iron and arsenic. It would appear, from the results of the liver treatment described, that these injections are no longer necessary.

Treatment of
Concomitants
Ankylostomiasis
Malaria, etc.

S U M M A R Y.

Sprue is a disease affecting Europeans mainly, who live in certain parts of the tropics. The endemic areas have mostly a hot damp climate and prolonged residence under such conditions is a predisposing factor. Lowered resistance from any debilitating condition increases the liability to contract the disease. The origin of the disease has not yet been definitely established although evidence points to the infection of the alimentary canal by some micro-organism. Two different organisms have been claimed as the cause of the disease, the monilia psilosis and the streptococcus. In the case of the monilia, proof is lacking that it is not a secondary infection on an already weakened intestinal mucosa. In the case of the streptococcus, it has not been possible to distinguish it from the streptococci, normally inhabiting the alimentary canal. The other suggested causes, calcium deficiency, vitamine deficiency and lymphatic obstruction might all have been brought about by an infection of the gastro-intestinal tract.

Sprue and pernicious anaemia have been compared. They have been looked on by some as different manifestations /

manifestations of a common toxin. The more general opinion, however, is that, though having several features in common, they are distinct clinical entities. Symptoms common to both diseases have been known to be caused by various intestinal parasites.

The pathological condition present is that of a chronic inflammation extending throughout the whole length of the alimentary canal. The mouth and small intestine are most affected. The fat content of the stools is increased and there is a relative increase in the amount of fatty acids present. Hydrobilirubin is reduced to a colourless compound leucobilin. The cholesterol content of the blood and bile are lowered. The pancreatic functions are more affected in some cases than in others. There may be an over stimulation of the pancreas to start with, as evidenced by the excessive splitting up of neutral fats into fatty acids. In the later stages there is a diminution in the output of pancreatic ferments. Free hydrochloric acid in the stomach tends to be increased in the early stages of the disease and diminished in the later stages.

In the blood, anaemia of the pernicious type does not appear, until the disease is well advanced. Nucleated red cells are rare and there is little evidence of any erythroblastic response on the part of the bone marrow.

There/

There is a definite deficiency in the calcium content of the blood. First the amount of free calcium is reduced by being transformed into combined calcium. Later the total calcium is reduced. The reduction of free calcium in the blood is directly proportional to the severity of the disease.

The typical symptoms are diarrhoea with large, pale coloured, frothy motions and sore mouth and tongue. The gradual atrophy of the filiform papillae of the tongue leaves the fungiform papillae standing out prominently. These classical symptoms may not be present in the earliest stages of the disease. A slight looseness of the bowels lasting a few days may be the only initial symptom. The earlier the condition is recognised the more easily is it cured. If bacteriological examination of the stool is negative, any recurrent diarrhoea, associated with loss of weight and lowered ionic calcium content of the blood, should be considered an indication of sprue and treated as such without waiting for further symptoms to develop.

In treatment a graduated milk diet is generally recognised as the most useful for those patients who can take it. Meat and fruit may be added as the patient improves. Medication with calcium lactate and parathyroid extract has proved a great advance in modern treatment, especially in early cases. The use of/

of autogenous vaccines has not been attended with marked success in the hands of the majority of workers and the same may be said about yellow santonin.

In the writer's practice treatment with raw liver and liver extract caused improvement where other remedies had failed. Where there was marked involvement of the pancreas the addition of pancreatic extract caused more rapid recovery. Four cases treated with raw liver and six cases treated with liver and pancreatic extracts recovered their normal health and kept well while in the tropics for periods of from one to two years.

CONCLUSIONS.

1. That the early recognition of sprue is of the utmost importance.
 2. That the ionic calcium content of the blood is a valuable aid to diagnosis and estimation of progress.
 3. That parathyroid extract and calcium lactate are valuable remedies in treatment, especially in early cases.
 4. That pernicious anaemia and sprue are separate diseases.
 5. That treatment with raw liver or liver extract is of distinct benefit especially where there is severe anaemia.
 6. That the addition of pancreatic extract to the liver extract is necessary where there is marked pancreatic deficiency.
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