A CASE OF PERNICIOUS ANÆMIA

WITH OBSERVATIONS REGARDING

MODE OF ONSET, CLINICAL FEATURES, INFECTIVE NATURE, PROGNOSIS, AND ANTISEPTIC AND SERUM TREATMENT OF THE DISEASE

BY

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Notes of Case.

Case 1 (*Charing Cross Hospital*).—Name of patient, A. L—, aged 37; occupation, traveller; admission, July 4th, 1900.

Complaint on admission.—"Great weakness, breathlessness, and palpitation."

Duration.—About two years.

Family history.—Father died at thirty-seven from the effects of a *stroke of lightning*. Mother alive and well, sixty-three years old. Two brothers alive and well. Three sisters also alive and well. One sister died of cancer of breast at thirty-six years of age. Nothing else of importance in family history.

Past personal history.—(*a*) Twenty years ago the patient, while killing pigs condemned for swine fever, was inoculated by a wound in the finger. He was very ill for a few days, with high temperature, urticaria-like rash on the body surface,

great swelling, etc., but eventually recovered completely. (*b*) He had typhoid fever while a child. Recovery complete. (*c*) Four years ago he suffered from three accidents, all within a short space of time, viz.:—(1) Head injury caused by falling out of a trap; (2) kick from a horse over the left eye; (3) kick from a horse over the spleen. He seems to have recovered almost completely from all these injuries, the only indications nowadays being occasional sensations of numbness in the regions of the first two injuries, and a certain tendency or liability to headaches upon slight provocation, such as an unusual amount of brain-work (calculations, etc.), excitement, or irritation; and, again, he is liable to giddiness on stooping down for any length of time. (*d*) He has also suffered from influenza twice, the first occasion being three years ago, when his principal symptoms were "head;" and again six months ago, when they were again most prominent, and after which his present condition became much more aggravated.

Habits and general surroundings always seem to have been excellent. He describes himself as being a very "careful living man," particular about his food, health, and general comforts. He always appears to have been in a position to gratify these desires. He has passed through several grades of occupation:—(1) He began life on his father's farm in Bedfordshire; then became (2) butcher at Kilburn for three years; (3) charge of stables at Bon Marché for twelve years; (4) bought a public laundry for himself at Willesden, and kept this going well until April of this year, when he gave it up, owing to the great decline in his general health and consequent inability, through weakness, to give that care and attention to his business which was essential for its success. Latterly he has had a very easy and profitable occupation as a traveller for a brewery in Kilburn, which gives him very little anxiety and exertion; but even this he has recently been compelled to give up.

Present illness began two years ago, when the patient noticed his appetite was poor, weight coming down; colour, which had always been red, disappearing and becoming yellowish at times, and what was most prominent of all, an almost constant pain in the stomach and side (over spleen), and periodically acute attacks of *severe pains in the mouth and stomach.* On investigation still further into these curious periodical attacks of pain which he complained of, it was ascertained that at this time

(two years ago) he was greatly troubled by what he describes as a *sore mouth*. It began by pain and swelling of the gums, then the teeth became sharp-edged in feeling, so that they tasted like "china" in his mouth, and seemed as if they would at any moment cut his tongue to pieces. In twenty-four hours after this the tongue itself would become almost unbearably sore, and on inspection patient noticed big red patches on the dorsum and edges. In endeavouring to describe the sensation of this sore mouth, he said:—"The tongue felt as if it had no covering, as if it was quite raw, so that when I put a piece of bread in my mouth at meals it felt like sandpaper." It never seems to have bled; and it is interesting to notice that when the attack, which usually lasted two or three days, was over the patient could eat beef-steak or any other food. During the attack his food consisted of milk and bread sop. The attacks came on about every three weeks, and were followed and accompanied by gastric symptoms, which will be referred to later.

This state of matters continued until about Christmas, 1899, when patient had three very bad teeth extracted; and he is certain that from that date the mouth condition diminished very considerably in severity. He has had mild complaints since; but *the* complaint which has been most prominent since that time has been the *gastric pains*. He has constantly suffered during the last twelve to eighteen months from a gripping, vice-like pain in the region of the epigastrium, always more marked at times, *e. g.* after a mouth attack, when he had worked hard and exhausted himself, or when annoyed or irritated by anything. His appetite was very variable, depending to a great extent upon the condition of his mouth, but always improved after the mouth trouble was over for a time (interval between two attacks). He has had recently a tendency to *nausea*, which became aggravated in its severity when anything unpleasant or distasteful to sight, smell, or taste was present. He was never actually sick, except after taking some medicine which he had had during an intermittent illness (influenza). Nausea and *retching* were often present, and the latter was particularly severe if the stomach was empty.

During the last twelve months the patient has felt himself grow perceptibly weaker, and incapable of hard work.

Breathlessness, palpitation, and giddiness have gradually forced

themselves upon him; and now he can distinctly recollect how he has noticed the gradual onset of the *lemon yellow colour* of skin all over the body, but states that it has constantly varied in intensity. The most marked features of late have been the great *weakness*, together with the nausea, etc., referred to above; and in addition, *pains shooting down the limbs, numbness, tingling in the shins*, acute pains in the clavicular regions at times which almost arrested breathing. The patient has been treated all along for chronic catarrh of the stomach, and his mouth has been relieved by borax, glycerine, and chlorate of potash lozenges. His diet was never the subject of special comment; he generally took what he thought would suit him. He came to Charing Cross Hospital on June 29th for examination, and after hearing the history and examining the blood, the case was diagnosed as "Pernicious Anæmia," and was recommended to come in as soon as possible for treatment.

Condition on admission (July 4th, 1900).—Height, 5 feet 6 inches; weight, 9 stones 7 lbs. Appearance:—fairly well nourished; very anæmic; slight lemon colour.

Alimentary system.—History: oral, gastric, and intestinal—as above described.

Teeth.—Two incisors, lower jaw, exposed and carious at their necks; gums receding, inflamed. Necks covered with tartar. They have been in this condition for ten years, and have bothered him.

Upper jaw: right side.—Bicuspids and two molars absent, Wisdom tooth remains; shows carious cavity, and gum around slightly swollen and inflamed. *Left side.*—Canine represented by a necrotic root. *Lower jaw.*—Back tooth, left side, represented by a rotten root. Other teeth sound. *Tongue* normal, gums somewhat anæmic; otherwise normal. The *stomach* slightly enlarged; complains of localised severe pains over the epigastrium. Patient cannot bear the least pressure here. The *liver* quite normal. *Spleen* slightly enlarged. *Bowels* somewhat loose, and fæces paler than normal.

(2) *Circulatory system.—Heart* slightly enlarged in its transverse diameter. Over pulmonary and mitral areas systolic murmurs, soft and low in character.

(3) *Respiratory system*, with the exception of the breathlessness, normal.

(4) *Nervous system.*—Complains of tingling and numbness, shooting pains, etc., as described above.

(5) *Urinary system.*—Urine dark sherry in colour; urobilin; no albumen, or bile, or sugar.

(6) *The conditions observed in the blood.*—The red blood-corpuscles were markedly altered in size and shape, showing poikilocytosis; numerous nucleated R.B.C. were present. Hæmoglobin 35 per cent., and R.B.C. 1,500,000 per c.mm. (30 per cent.).

Progress of Case.

Period 1 (July 4th to 9th).—*Treatment.*—Patient was put upon milk diet; an antiseptic mouth wash; liq. hydrarg. perchlorid., ♏xxx, thrice daily as an intestinal antiseptic; with carbonate of ammonium (gr. 3), and tincture of digitalis ♏v as a stimulant.

July 6th.—Patient had an attack of sickness yesterday, preceded by much pain in the usual situation, at 4 p.m., about quarter hour after taking medicine (vomit bilious in character, according to patient), after which he was all right and had a good night's rest. This morning he feels very sore in the stomach, and legs ache very much from knee to ground. The tongue has a prickly feeling, which makes it feel "as if it were clinging to roof of mouth." On examination, nothing is made out except a *small red patch in the middle line,* almost at position of hard and soft palate; patient puts his fingers on it and says it is "*raw.*"

Blood.—Examination on July 6th. Great difficulty was experienced this morning in getting away blood at all for examination. On puncturing the fingers scarcely a drop came away; and it was only on pressure to the part, and allowing hand to hang before puncture, that any was forthcoming.

7th.—Blood examination this morning showed red corpuscles 1,350,000 (27 per cent.), with distinct poikilocytosis, and many nucleated reds were seen. Pain in the side (spleen) and stomach, continue as before. Feet very cold; mouth distinctly better; no sign of irritation.

8th.—Better this morning; pain in stomach and side easier, but still present in limbs; mouth quite easy; wash has improved it.

9th.—Patient feels unwell this morning; complains of pain

in limbs (usual situation), stomach, and heart—described as a "feeling of wind with pains like pressure;" the mouth is causing some trouble by pains around the first premolar on left side; the local signs of condition are *nil.* The stomach is dilated slightly. Temperature 99·4°.

Urine high-coloured.

Temperature.—(See Chart.[1]) *Blood.*—Corpuscles 27 per cent.

Period 2 (July 10th to August 16th = five weeks).—*Treatment* as above, *plus* four injections of antistreptococcic serum.

10th.—*First injection* of antistreptococcic serum made, 10 c.c., at 6 p.m. last night.

Patient feels tired and worn out this morning; has passed a sleepless night. Temperature 99°. Pains are complained of all over body, particularly over right side, and stomach and legs. He looks flushed. Pulse 98. Mouth "dry"—nothing obvious on examination.

11th.—Patient feels distinctly unwell to-day. Temperature 101·6°; complains of pains in right side of stomach (hot burning), and slightly on left side. Pulse 120. Headache severe.

12th.—Temperature 102·6°; pulse 120. Although temperature and pulse are still high, the patient does not feel anything like as unwell to-day as yesterday. The principal complaint is headache, felt principally at vertex; pains in stomach and side as before; complains also of flatulence and retching, although food is still peptonized; mouth is very dry (lemon drink given); great thirst. Legs remain the same, and arms also ache badly. Throbbing pains, lightning like. Blood examination, corpuscles 1,580,000 (31 per cent.). Hæmoglobin 35 per cent.

13th.—Temperature 99°; pulse 100. Patient feels more himself to-day. Headache has passed to occiput, and is not so severe. The pain in stomach, side, and limbs is better. Motions are liquid. Mouth better.

Blood.—Corpuscles 31 per cent. Hæmoglobin 35 per cent. Second injection of serum at 8 p.m.

14th.—Rigor for quarter hour at 1 a.m; sleepless and restless night. Feels better this morning—very little pain complained of. The rigor started in left shoulder, and passed down whole left side. Right side unaffected.

[1] For chart of this case see author's 'Pernicious Anæmia,' Charles Griffin and Co., 1901.

15th.—Temp. 100·2°. Complains of severe pains in head. Otherwise as before; slept well; appetite good.

16th.—Temp. 100·8°; pulse 96. Blood 1,800,000 (36 per cent.). Hæmoglobin not estimated. Great difficulty experienced in getting blood for ordinary numerical estimation. Pains and discomfort are complained of. Motions are more solid; liq. hydrarg. perchlor. is reduced.

17th.—Temp. 99·2°; pulse 88. Headache not so violent, but with sharp pains; soreness on left side from point of last injection down left groin and leg. Mouth and tongue not sore to-day. Patient has difficulty of passing water lying on his back.

20th.—Patient feels much better. His head feels better, but complains of sweating on his head. Soreness in side is better, and no difficulty in passing water. Temp. (10 a.m.) 98·4°; pulse 76. Corpuscles 2,530,000 (50 per cent.).

21st.—Patient describes himself as better altogether.

22nd.—Third injection (5 c.c.).

23rd.—*Blood-count*, 2,635,000 (52 per cent.). Blood flowing much more easily than formerly. The corpuscles were noticed to be more even in shape, approaching more nearly the normal cells. Hæmoglobin obviously more abundant, but not estimated. Patient describes himself as improving. Sleeps well. Temperature normal.

25th.—Patient improving daily. Temperature steady (see Chart). Yesterday food changed; more solid nature; fish, etc. Patient relishes the change. All aches, pains, etc., have disappeared of late.

31st.—Patient has not felt so well since Saturday, 28th. Complains of pains in head, feeling of thickness or dulness. Stiffness in shoulders and neck, soreness under ribs. Some palpitation on movement. Skin all over body is clearer. There is a certain amount of rawness in the perineal region—an old complaint which patient suffers from periodically. *Blood-count* 2,845,000 (56 per cent.).

August 1st.—Blood:—(W.H.) R.B.C. 3,290,000 (65 per cent.), W.B.C. 17,000. Hæmoglobin 75 per cent. Patient greatly improved in looks.

2nd, 11 a.m.—Last night, fourth injection (5 c.c.). Afterwards no sleep until 4 a.m., when he had an hour's sleep. (Trional grs. xx given, before grs. x with no effect)—slept

again this morning—appetite fairly good—complains chiefly of pain in the left side, near seat of injection and passing into flank; looks flushed. Temperature practically normal (98·6°). Pulse 120. Headache improved.

3.30 p.m.—Patient feels much better this afternoon.

3rd.—Temp. 99° this morning; slight reaction has set in after the injection on the 1st. Pulse 120. Patient feels better to-day.

4th.—Pulse 120. Temperature last night rose to 99·8°. Now 99°; slept well. Troubled with headache. Complains of flatulence after food. Locally, still some brawny œdema, left flank, close to site of injection. *Urine.*—High colour, heavy deposit of red urates.

7th.—Feeling better; up each day from 12 to 6 p.m. Looking well. Pulse 84. *Urine normal in colour. Much lighter than any time since admission.* Blood 2,750,000 (55 per cent.). Hæmoglobin 70 per cent. Slight looseness of bowels to-day (twice).

8th.—Two lower incisors, formerly described, edges red and inflamed, and *covered with pus*, despite the fact that he has used an antiseptic mouth wash daily for a month. Swabbed out with 1 to 20 carbolic acid. Edges bleed freely. Tartar removed. Gums to be swabbed daily with 1 to 20. Slight desquamation of skin over face. No local tenderness over abdomen. Pulse 78. Temp. 97·8°. *Urine.*—Straw colour. Sp. gr. 1018. No albumen.

10th.—Blood examined. Corpuscles 3,360,000 (67 per cent.). Hæmoglobin 72 per cent. Corpuscles normal in appearance. *Feeling very well.*

15th.—Three teeth drawn. Back wisdom upper jaw; lower jaw left wisdom; upper canine. *Lower incisors.*—Gums previously receding, now grown up around tooth and looking healthy. They have not been right, he says, for ten years.

16th.—Patient goes out to-day. Pulse 84. Appetite good. Temp. 99°. Urine darker, 1025. No albumen. No indican.

Results of Five Weeks' Treatment.

Urine.—Very pale: urates appeared in urine on the first and second days succeeding injections.

(6) *Blood.*—	R.B.C.	Hæmoglobin.
July 4th	1,500,000 (30 per cent.)	35 per cent.
„ 7th	1,350,000 (27 „	
1st inject.:		
„ 9th		
„ 12th	1,580,000 (31 „)	35 „
2nd inject.:		
„ 13th		
„ 16th	1,800,000 (36 „)	
„ 20th	2,530,000 (50 „)	
3rd inject.:		
„ 23rd	2,635,000 (52 „)	50 „
„ 31st	2,845,000 (56 „)	
4th inject.:		
Aug. 1st	3,290,000 (64 „)	75 „
	W.B.C. 17,000 per cmm.	
„ 7th	2,750,000 (55 per cent.)	70 „
„ 10th	3,360,000 (67 „)	72 „
	R.B.C. normal; no poikilocytosis.	

Total result in blood.—An increase of 40 per cent. of red corpuscles and 37 per cent. of hæmoglobin.

Period 3 (August 16th—September 26th = six weeks).—Sent to the country. *Treatment.*—Oral and intestinal antisepsis as before. Light ordinary food, chiefly milk. ʒj of Syrup of Hypophosphites three times daily as a tonic. Arsenic still withheld.

September 26th, 1900.—Returned. Looking stout. He has put on 7 lbs. in weight. Weight is now 10 stone. Good colour. Complains still of numbness and dead feeling of finger-ends. Mouth and teeth very clean. Digestion normal.

Blood.—Red corpuscles 3,200,000 (64 per cent.). Hæmoglobin 80 per cent.

Result.—The improvement in weight, colour, and appearance is greater than the improvement in blood. The latter only shows an increase of 8 per cent. in hæmoglobin.

Period 4 (September 27th—November 8th = six weeks):—*Treatment.*—Oral and intestinal antisepsis as before. *Medicine.*—Liquor Arsenicalis ♏iiss ter die.

October 4th, 1900.—Looking still better, and feeling very well. Weight 10 stone 2 lbs. Appetite good; stomach com-

fortable. Bowels regular, generally once, and sometimes thrice daily. Urine pale straw-colour. He notes himself "it is much better;" that sometimes it is very dark, *e. g.* last week; and that it is always darker when he is not feeling very well.

His tongue looks red. He states it has been very sore last four days. "Feels cracked all over" when he takes anything to eat or drink. Last attack of the kind was four weeks ago, lasting about a week.

His chief trouble now is that his fingers feel perfectly numb, so much so that he cannot button his clothes, owing to want of feeling in fingers. This affects both hands, and extends up to elbows. Calves of legs feel weak, but there is no numbness in them.

November 8th, 1900.—Improvement still continues. Looks ruddy and stout. Weight 11 stone 2 lbs. (an increase of a stone in one month.

Blood.—Red corpuscles 4,040,000 (80 per cent.). Hæmoglobin 90 per cent. = increase of 16 per cent. in corpuscles, and 10 per cent. in hæmoglobin.

Period 5.—Further progress (November 8th—January 17th, 1901 = 10 weeks). *Treatment* as before. Arsenic increased to ♏v till December 21st, then reduced to ♏iis.

December 21st, 1900.—Looking very well. Weight 11 stone 2½ lbs.

Blood.—Red corpuscles 4,500,000 (90 per cent.). Hæmoglobin 92 per cent.

January 17th, 1901.—Looks in robust health.

Blood.—Red corpuscles 4,550,000 (91 per cent.). Hæmoglobin 104 per cent.

Tongue clean. Digestion good. Urine pale. Only symptom remaining is slight numbness in the tips of his fingers.

Remarks.

The case is of interest in connection with the result under the special line of treatment employed. But it is of additional interest—and for that reason is now brought before this Society—inasmuch as it presents in itself every clinical feature which I consider characteristic of this disease, as regards—

(1) Its antecedent history.
(2) Mode of onset.
(3) Character of its blood-changes.
(4) Character and grouping of its symptoms.
(5) Diagnostic features.
(6) Infective nature of the disease, and its relation to oral and gastric sepsis.
(7) Its response to a special line of treatment, based upon my observations regarding the infective origin and seat of infection of the disease.

Conclusions regarding the Nature of the Disease.

The following are the conclusions I have arrived at as the result of fifteen years' investigations—histological, experimental, chemical, clinical, and ætiological—regarding the nature of this disease.

1. Pernicious anæmia is a chronic infective disease of septic origin.

2. It is the result of a special infection of the mucosa of the digestive tract, especially of the stomach; frequently also of the tongue, and of the intestine.

3. The effects are chronic infective lesions of the tongue and stomach or intestine, which can be seen (in the tongue) to heal up in one part only to spread to another, causing in time deeper-seated changes, *e. g.* ulcers of the mouth and tongue, chronic glossitis and atrophic changes in the tongue; gastritis with atrophy of gastric glands; and localised enteritis.

4. In this infection, oral sepsis arising in connection with long-continued and neglected cario-necrotic conditions of teeth plays an essentially important antecedent and concurrent part by creating the local conditions of the mucosa ("septic" stomatitis, gastritis, and enteritis), which permit the infection to take root.

5. In the vomit the septic nature of the catarrh of stomach can be demonstrated in every case.

6. One element in the infection (in pernicious anæmia) is streptococcal; but this is not the only one. It

probably derives its special (hæmolytic) properties from being of a "mixed" character.

7. For the infection to occur it is essential that the mouth, stomach, or intestine be already from some cause the seat of disease; the most potent antecedent cause is "oral sepsis," and "septic gastritis" arising in connection with oral sepsis.

8. The gastric and intestinal symptoms—sickness, retching, vomiting, looseness of bowels, and diarrhœa—so often noticed (and I find even more common than is stated, being recorded in over 80 per cent. of cases) are the local manifestations of the infection; while the excessive destruction of blood taking place in the portal area is the result of the action of its poisons absorbed into the blood.

9. The fever so commonly met with is not an accidental occurrence—the effect of weakness,—but is a feature of the disease, a result of the infective process itself; and its variations correspond to variations in the activity of that process.

10. Such variations are common—from week to week, sometimes from day to day—in the progress of the disease, even when it is running a fairly progressive course.

11. In addition, however, the course of the disease towards the fatal termination is often marked by one—sometimes by two—periods of marked improvement, lasting, it may be, many months, or a year or more, followed by relapses. This character of the disease I have come to regard as the result of a relative immunity, unfortunately only temporary in its nature, conferred by the disease itself—an immunity accelerated and greatly strengthened for a time by suitable medicinal treatment, notably by administration of arsenic.

12. The tendency to relapse may, however, be due to the fact that, hitherto, the immediate sources of infection, viz. the oral sepsis, not having been removed, the patient has always been left exposed to reinfection.

Gastro-intestinal Site and Infective Nature of the Disease.

On this point, the most important of all in connection with the disease, the conclusions I have formed are, as already mentioned, of a very definite character.

The disease, I conclude, is not only a special form of anæmia, but a most definite infective disease, localised to the mucosa of the alimentary canal, causing a most definite and characteristic group of effects, both clinical and pathological, which enable it to be distinguished during life and after death.

In this infection sepsis, both oral and gastric, plays an important antecedent and concurrent part.

These conclusions are of such a character, that if taken by themselves, without regard to the continuous line of investigations on which they are based, one might perhaps doubt whether they could possibly refer to the disease originally described by Addison as "idiopathic, —occurring without any discoverable cause whatever;" and subsequently defined by Dr. Pye-Smith (1883), on the strength of the facts supplied by thirty years' additional observations, "primary, autochthonous—without any symptoms, and without any lesions that cannot be explained as directly due to the anæmia."

And yet it is to this anæmia that the conclusions refer. Moreover, it is to this alone—the so-called "primary" "cryptogenetic" form of the disease. The "secondary" forms described by Biermer, Eichhorst, Ehrlich, are in my experience totally distinct conditions.

I recognise no "primary" or "secondary" forms of the disease, any more than I recognise primary and secondary forms of typhoid fever or tuberculosis. As with other infective diseases so with this one ("Addison's anæmia") there is no reason why it may not occasionally occur in patients already the subjects of other diseases; but even when it does, it can be recognised by its definite

clinical features as clearly as if it occurred alone, just as typhoid fever can be recognised, although occurring in a patient the subject of tuberculous disease.

In the accompanying scheme I have represented graphically the course and results of the investigations —histological, experimental, chemical, clinical, and ætiological—extending over fifteen years, on which the above conclusions have been based.

Full details are given in my work 'Pernicious Anæmia,' C. Griffin and Co., 1901.

In no case have the conclusions been lightly formed; and they differ from most other conclusions regarding the ætiology of the disease in this respect—that while most others are based on clinical grounds only, the basis of these is essentially pathological. It is the series of investigations regarding—

(1) The Hæmolytic Nature of the disease;

(2) The Special Character of the hæmolysis;

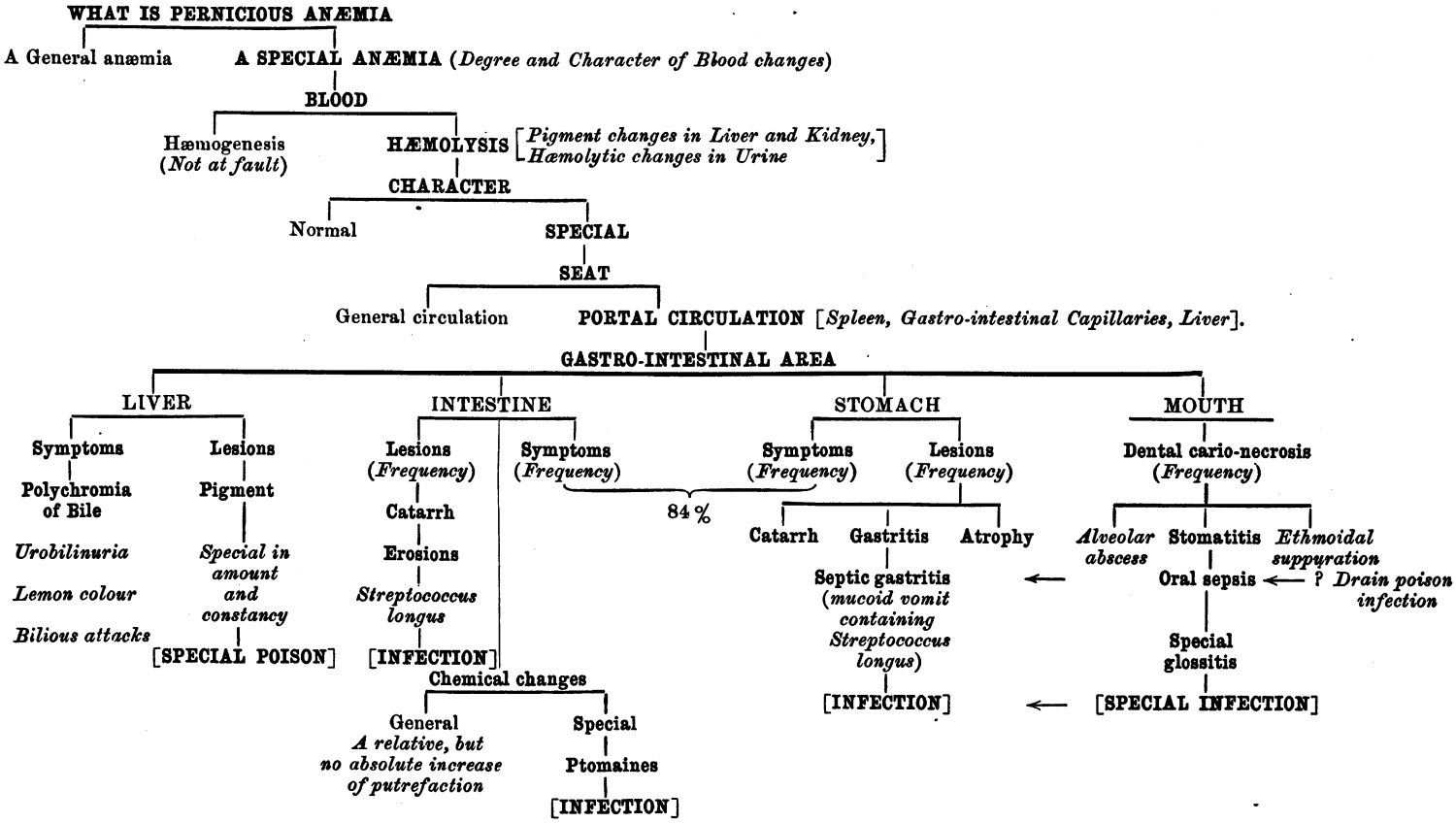
(3) The Portal Circulation as its seat;

that constitute the basis of my conclusion regarding the special nature and gastro-intestinal site of the disease processes underlying the hæmolysis of this disease.

And all my later observations and conclusions and studies regarding the frequency, character, and possible significance of the symptoms and lesions connected with this tract, derive their importance in my eyes chiefly, if not solely, from the circumstance that they are in entire agreement with these pathological conclusions (see Scheme).

Without the basis here indicated, it would not be justifiable, for example, to attach to the whole group of oral, gastric, and intestinal symptoms, and to the special lesions met with in the tongue, the significance I now do, as denoting the existence of a special infection in this tract.

SCHEMATIC REPRESENTATION OF COURSE AND RESULTS OF AUTHOR'S PATHOLOGICAL INVESTIGATIONS REGARDING THE HÆMOLYTIC NATURE, GASTRO-INTESTINAL SITE, AND INFECTIVE ORIGIN OF PERNICIOUS ANÆMIA.



Definition of the Disease.

Hitherto the feature of the disease to arrest chief attention has naturally been the *anæmia*—the progressive blood change,—and all other symptoms have been studied in relation to this. The disease has been regarded as an anæmia complicated from time to time by other disturbances—digestive, nervous, circulatory, etc. The result has been to obscure some of the chief characters of the disease, and certainly to hide much of their proper relation to each other. The conclusion I have come to is, that it is an *infective disease characterised by anæmia* with *definite local and general* effects—not merely an anæmia occasionally complicated with such effects.

The definition which I have formulated for the disease is the following:

Pernicious anæmia is a chronic infective disease localised to the alimentary tract, *caused by* a definite infection of certain parts of the mucosa of the alimentary tract either of the stomach, tongue or the intestine. In this infection, sepsis, both oral and gastric, plays an essentially important antecedent and concurrent part. It is *characterised by*—

(1) Intermittent destruction of blood and increasing anæmia (and all the other pathological and clinical changes consecutive to these—*e. g.* anæmia, lemon colour, urobilinuria, hæmorrhages, dyspnœa, palpitation, œdema), as the result of the absorption and hæmolytic action of poisons into the blood.

(2) Periodic disturbance of the alimentary tract—tongue, stomach, or the intestine—as local effects of the infection in the alimentary canal; and

(3) Occasional "toxæmic" attacks, characterised by fever, sweatings, general nervous symptoms; not infrequently by effects—*e. g.* numbness, tingling, ataxia, absence of reflexes—denoting deeper nervous changes, such as peripheral neuritis, sclerosis of the cord.

The foregoing characters of the disease are well represented in the case described, and I shall comment on them in the order mentioned.

Antecedent History.

The patient was a "careful living man," who had always enjoyed good health, and had been well fed and nourished.

Such a history is, in my experience, one of the striking peculiarities of the disease, namely, it occurs, as Addison described, "without apparently any discoverable cause."

In my experience, it is met with in the well-to-do as much as in the poor, in the well-fed as much as in the poorly nourished, in the athletic man as much as in the weakly, in the man who has spent his whole life in the country as much as in those living in towns, in those whose health has previously been good (as in the present case) no less than in those already debilitated by disease.

It is this class of facts that has satisfied me that in the production of this form of anæmia general conditions of life are not those at fault; that its origin is to be sought elsewhere—in some special conditions, rare, fortunately, in incidence, but common to all classes, irrespective of station, mode of life, character of food, of nutrition, or general surroundings.

That special condition my observations show to be a special infection, localised to portions of the mucosa of the alimentary tract, having its chief seats in the tongue and in the stomach, an infection in which long-standing sepsis, oral and gastric, plays an essentially important antecedent and concurrent part.

In his original description of the disease—that the disease occurred in the absence of the ordinary factors causing anæmia—Addison, then, in my judgment laid,

the ætiological foundation of our knowledge of this disease broad and deep.

The different conclusion come to by Biermer, so largely accepted by nearly all later observers—namely, that all ordinary causes of anæmia are potential causes of this disease, if only they are severe enough—has, in my experience of the disease, no real basis. The disease cannot, in my experience, be produced by ordinary anæmia-producing factors, however severe; and cases of this kind can be successfully excluded, both during life and after death, by the absence of the characteristic groups of symptoms, and of the no less characteristic pigment changes I have described.

Mode of Onset.

A gradual onset of anæmia, weakness, breathlessness, and palpitation, dating from about two years before he came under notice—without any obvious cause, and especially marked during the last twelve months. The only special symptoms were those connected with his stomach, namely, epigastric pain with tendency to nausea and retching, especially if stomach were empty; so that he was treated throughout as one suffering from chronic gastric catarrh.

On the top of these comparatively mild gastric symptoms there developed a degree of anæmia and weakness *out of all proportion* to the severity of any apparent cause, the anæmia so great that when he was first seen the corpuscles were reduced to 30 per cent., and his hæmoglobin to 35 per cent.

This relation of events—a history of antecedent gastric or intestinal trouble extending usually over many years, *more or less suddenly followed by a rapidly developing anæmia out of all proportion to the actual extent or severity of symptoms or lesions existing in the stomach or intestine*—such is, in my experience, the typical mode of

development of pernicious anæmia. This more or less suddenness of development, with the extraordinarily high degree of anæmia (exceeding anything ever met with even in the severest forms of wasting anæmia), are the clinical features which I have come to regard as denoting the supervention of a new factor—viz. definite infection of some part or other of the alimentary canal.

It is this history that leads me to inquire minutely into the character of the oral (especially tongue) symptoms at the very outset of the illness.

In the present case the account gathered from the patient is singularly clear. He had a history of oral sepsis extending back for ten years. At the very outset of his anæmia, he was greatly troubled with a "sore mouth," and I refer to the account itself for the remarkable history given of the persistency, painfulness, and above all *periodicity* of the glossitis there described, the attacks coming on every three weeks or so, accompanied by the gastric symptoms already referred to.

I shall again recur to the character of these tongue symptoms and their significance. For the present, what I wish to draw particular attention to is their *relation to the onset of the illness*—namely, they occurred as one of the first symptoms, when his anæmia and weakness were only commencing.

This is the point to which I recently drew attention ('Lancet,' January, 1900). As I have described in seven cases I have there recorded—

"*Mode of onset.*—The origin of the glossitis was in all cases as mysterious, and sometimes as sudden, as the weakness itself. The conditions were not simply the result of the anæmia. On the contrary, when they were of a character (by discomfort or painfulness) to attract the attention of the patient, they were always noticed at the onset of the disease or early in its course; and in most cases they actually subsided as the anæmia progressed. So closely connected were they, indeed, with the origin of the disease, that in three cases they were

among the first symptoms noticed and complained of; and in three cases the patients dated their weakness from the onset of the trouble in the mouth."

Additional Cases.

Since the foregoing was written in January, 1900, the following additional cases have been observed by me, and will serve to emphasise the points above mentioned with regard to relation to onset, characters, and periodicity of this characteristic glossitis.

Case I (the one now described).—Illness began two years ago; pallor, lemon-colour, constant pain in the stomach and side (over spleen), and periodical attacks of severe pain in the mouth and stomach. At this time he was greatly troubled with "a sore mouth." It began by pain and swelling of the gums; the teeth became to the feel sharp-edged, and felt as if they cut his tongue. In twenty-four hours after this the tongue itself became almost unbearably sore, and on examination showed big red patches on the dorsum and edges.

His tongue felt "as if it had no covering; as if it was quite raw, so that when I put a piece of bread in my mouth, it felt like sand-paper." The attack usually lasted two or three days, after which the patient could eat beefsteak or anything else. The attacks came on almost every three weeks, and were always followed or accompanied by gastric symptoms. This continued till Christmas, 1899. He had then three very bad teeth extracted, since which time the mouth condition has been considerably less.

Case 2.—"For a fortnight at onset of illness great soreness of tongue, necessitating use of a soothing mouth wash." A condition of extreme dental caries; only six good teeth remaining; ten rotten stumps in gums; other teeth absent. (A typical case of pernicious anæmia, with intense anæmia and urobilinuria.)

Case 3.—Ill-health began four years ago, end of 1896. In February, 1897, sore throat with considerable pain on swallowing, the pain seemed to run down into stomach. This lasted

for fourteen to twenty-one days, when it disappeared. Since then he has had slight attacks of sore throat at varying intervals up to the present time. End of 1897 first had trouble with his tongue, slightly swollen around the edges, with severe longish patches of a deep red colour, extremely tender. A few patches on the dorsum, less numerous and painful than those on the edges. Tongue very tender, especially to warm liquids. It got well in about a week's time. He has had repeated attacks of sore tongue since then, about once every two or three weeks, up till the last nine months, since which they have been slighter and at longer intervals (every two months). Since beginning of this year (1900) has hardly noticed anything wrong with his tongue.

On admission, tongue slightly red, with a few transverse cracks, edges rather glazed on the dorsum; not tender. Gums swollen and inflamed, projecting betwixt teeth. Teeth all in a very bad state of preservation, all the incisors and canines loose.

Under treatment with antiseptic mouth wash, redness of tongue rapidly disappeared. Seven weeks later tongue again became tender, red, showing small red granulations on its right edge. Temperature at same time rose a little; patient looked ill. This continued for nine days; then it lost its general red colour, but continued to show on its edges a number of angry red spots, size of a pin's head. (Death. Typical pigment changes.)

Case 4.—Three and a half months after illness began, patient noticed soreness of mouth and tongue. The degree of soreness has varied from time to time; at times the mouth causes no discomfort. During an attack the "tongue" "feels raw as if it had been cut." Dental caries and stomatitis. (Death from acute congestion of lungs. Typical pigment changes of pernicious anæmia in liver and kidneys, and bile.)

Case 5.—A lady æt. 39. Typical pernicious anæmia, as regards blood changes and characteristic grouping of features (hæmolytic, gastro-intestinal, nervous), I have above described.

At outset of illness, twelve months before, tongue very tender, necessitating soothing mouth wash.

The significance I attach to this glossitis is—

(1) It is not the result of the anæmia or weakness *per se*, for it often antedates the anæmia, or is most marked early in the disease.

(2) It is not an *ordinary* glossitis, such as is produced by ordinary oral sepsis. In the case now recorded, an attack occurred about a fortnight ago (February, 1901), notwithstanding that the patient's blood at the time showed 95 per cent. of corpuscles and 105 per cent. of hæmoglobin, and that there is no trace of oral sepsis.

(3) But it has special features, which denote that the tongue is the seat of a special infection which comes and goes, causing definite lesions. These lesions are at first small inflamed areas, denuded of epithelium, on sides or dorsum of tongue, sometimes showing angry red granulations, sometimes with formation of vesicles, sometimes resulting in linear cracks; in certain cases involving the whole tongue, so that it presents an angry red beefy look; in rare cases causing the tongue to swell up; in all cases resulting in atrophy of the mucosa, so that the tongue comes to present a very characteristic smooth polished appearance.

Another feature is its remarkable periodicity, coming and going in the most mysterious way independently of any obvious cause. This is, according to my observations, a notable character of every other clinical feature of the disease, even of the weakness itself.

Blood Changes.

On presenting himself the patient was found to have only 30 per cent. of red corpuscles, with 35 per cent. of hæmoglobin; that is, he had—

(1) A very high degree of oligocythæmia, far in excess of that producible by malignant disease alone, however long lasting, or by wasting disease; and produced without the intervention of hæmorrhage. This feature I regard

as highly characteristic of the blood change in pernicious anæmia; not distinctive in itself, if severe hæmorrhage have previously occurred, but highly distinctive when combined as it was in this case with—

(2) A relatively high hæmoglobin ratio of the individual corpuscles.

In my experience this high ratio is never met with in anæmia from loss of blood.

As I shall presently show, the diagnosis of the disease is not to be based upon the blood changes alone, but only upon these when taken in conjunction with the no less constant and characteristic groups of symptoms which I shall presently describe.

The chief significance I attach to this high degree of oligocythæmia is this :—In my judgment it denotes that hæmolysis is greatly increased, since according to my observations it is easy to produce the *highest degrees* of oligocythæmia by means of hæmolytic agents, while the experience of disease teaches clearly that this is not easy, even by repeated hæmorrhages, still less by wasting nutritional diseases, however profound.

Clinical Features.

As regards the *general* features which go to make up the clinical picture this disease presents, no description ever given can better the original one of Addison: a general anæmia occurring without any discoverable cause whatever; pursuing a similar course, and with scarcely a single exception, followed after a variable period by the same result; making its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of the languor which is shortly to become so extreme; increasing pallor; indisposition to exertion, with faintness or breathlessness on attempting it; bloodlessness of lips, gums, and tongue; failure of appetite, extreme languor and weakness, till the patient can no

longer rise from bed, and at length, sooner or later, falls into a prostrate and half-torpid state, in which he finally expires.

As regards the relation of these symptoms to one another, and to the anæmia, their essential feature appears at first sight to be, that one and all of them are referable to the anæmia. The latter appears "idiopathic, primary, essential, without any symptoms during life that cannot be explained as directly due to the anæmia" (Pye-Smith).

Even the *fever* so commonly met with appears to be "anæmic" in its character (Immermann); the *hæmorrhages*, likewise, are the result of fatty degeneration of the capillary walls, consequent on the anæmia; the *nervous disturbances*, psychical, sensory, or motor, such as are not infrequent, have been referred to the capillary bleedings in the nervous system (Eichhorst); and lastly, the *alimentary disturbances*, not infrequent, if only slight, seem merely results; if severe they appear to be possible aids in producing the disease, from the exhaustion and profound disturbances in nutrition they occasion (Biermer, Eichhorst, and Fenwick).

From the definition I have given it will be seen that, in the light of the foregoing studies, the various clinical features presented by the disease have, in my mind, assumed a somewhat different relation to one another.

I am accustomed to divide them into four groups, and these are well illustrated in the present case.

1. *General symptoms.*—A group which may be regarded as *effects* of the anæmia.

These include most of the more prominent features of the disease, such as *pallor, weakness, breathlessness, palpitation, irritability, sleeplessness, incapacity for mental or bodily exertion, want of appetite, feeble digestion, sluggish intestinal powers,* and lastly, the general normal *characters of the urine,* as regards quantity, excretion of urea, freedom from albumen, sugar, bile, blood.

Special symptoms. 2. *Hæmolytic.*—A group, the effect not of the anæmia itself, but of its *hæmolytic character.*

These include the *lemon colour,* varying greatly in intensity at different periods; the *urobilinuria,* with or without *high colour of the urine,* also varying greatly at different periods; occasionally also, deeply bile-stained fæces, likewise varying from time to time.

3. *Oral, gastric, and intestinal.*—A group related to the anæmia not as effect or as causes, but denoting *the site* of the lesion underlying the disease.

These include the *oral, gastric,* or *intestinal* symptoms, varying in intensity from time to time; insufficient of themselves to account for the anæmia; and not to be accounted for by any mere weakness resulting from the anæmia; but important as marking the existence of some special irritant trouble in the portions of the alimentary tract affected.

4. *Toxæmic.*—A group, like the last, neither cause nor effect of the anæmia *per se;* but denoting the toxic *character,* and infective nature of *the agencies* causing the anæmia.

These include most prominently of all, the *fever*—which comes and goes in the most varying manner, but is, in my opinion, rarely if ever absent in any case that is actually advancing. It also includes other phenomena, not so general but often met with, all of them characterised by the same periodicity which has been seen to be so common with most of the other features, namely, *headache, perspiration, drowsiness, languor, feelings of intense weakness,* and illness; also a group of more pronounced *nervous disturbances,* denoting actual lesions in central or peripheral nervous system, such as *pains, numbness,* and *tingling* in the arms and legs, *disturbances of sensibility, ataxic phenomena, loss of knee-jerk,* sometimes actual *peripheral palsies.*

It is the existence of all these groups of symptoms, in connection with a profound oligocythæmia, that consti-

tutes in my judgment the complete and characteristic clinical picture which this disease presents.

In my experience they are to be found in combination in every case of pernicious anæmia; they are all related to one another, although sometimes one or other may be specially prominent; and they have one marked feature in common, namely *periodicity*—the same feature which, as already seen, characterises the local lesions met with in the tongue.

In the present case these features were well exemplified.

Group 1.—General Clinical Features.

These I need not dwell upon. They comprise what are generally regarded as the chief, and by many the characteristic features of the disease, the symptoms for which the patient seeks advice—the weakness, breathlessness, palpitation, etc.

The relation between them and the poverty of blood seems obvious. They seem the direct result of the blood changes, and to be proportioned to these.

If they comprised, as they are held by many to comprise, the chief features of the disease, then the disease might apparently with reason be described as being without any symptoms other than those referable to the anæmia itself.

And yet with regard to many of these, I have to point out that they are only *in part*—not *wholly*—caused by the degree of anæmia present. That is to say, the weakness, lassitude, inability for exertion, breathlessness, palpitation, etc., are *not* always proportionate to the degree of anæmia present. On the contrary—

(1) *They may all be extremely marked, with a relatively good condition of blood;* and

(2) *They may all be absent, with a much poorer condition of blood.*

In other words, with regard even to these general features, *some other factor than mere degree of anæmia is at work.*

A patient may be *very ill* and weak, with over 60 per cent. of red corpuscles and hæmoglobin; while another may be actively going about and feeling well, with only one half that proportion. And even in the same patient at different times, he may be so ill that he can hardly walk or even sit up, with his blood showing 26 per cent. of corpuscles and 40 per cent. of hæmoglobin; and two months later he may be able to go about from morning to night, take walks, go up and down stairs, eat well, and describe himself as "feeling better than he had done for several years;" yet his blood show only 28 per cent. of corpuscles and 35 per cent. of hæmoglobin (Case 10, op. cit.).

I consider this a remarkable feature of the disease—one which demonstrates that the clinical features, even the simplest of them, are not referable to the degree of anæmia, and to that alone.

2. Hæmolytic Changes in the Urine.

These include high colour of the urine, marked by urobilinuria; the latter having, according to my observations (1889), certain special features which distinguish it from the urobilinuria of febrile disease.

Like all the other features this character of the urine is marked by *periodicity.* It is related to the degree of hæmolysis occurring, and this in turn to the activity of the infective process within the gastro-intestinal tract.

I show now samples of the urine from the case described from the time of admission, six months ago, up to the present time (January, 1901).

At the outset the colour was high.

It improved steadily, albeit slowly, for the first two weeks under his treatment; afterwards more markedly,

so that when he went out after five weeks it was of normal colour. It continued to vary for some time after; as the patient described it, "it was always darker when he was not feeling very well." It is now (January, 1901) pale and natural colour, although he possesses 104 per cent. of hæmoglobin and 90 per cent. of red corpuscles; whereas when his disease was in progress it was very dark, although he had only 35 per cent. of hæmoglobin and 30 per cent. of corpuscles.

This relation of urobilinuria to the general progress of the disease, and to the other clinical features (those comprised in Groups 1, 3, 4), I have brought out in a chart, which I now show, from another case which I had under continuous daily observation for some three months or more (see chart, op. cit.).

It can there be seen how closely the curve of urobilin followed the general progress of the disease; when the patient was well, the urine being almost colourless, so pale was it; while corresponding with his active attacks, characterised by sore tongue, vomiting, fever, lemon colour, and feelings of intense weakness, the urine was always higher in colour.

This relation of events was the feature I drew attention to in my original studies in 1889.

It is in my experience a very instructive one, if carefully observed over a period of time.

3. Oral, Gastric, and Intestinal Symptoms.

To the group of symptoms connected with the alimentary tract from the mouth downwards I attach a special interest and importance, and this not on account of their severity or persistence. The interest they have for me is their existence at all in connection with this tract. The basis of that interest is entirely pathological.

These gastric and intestinal symptoms have no other

characters than those recognised and described by the earliest observers of the disease; sometimes so severe as to appear to be the cause of the disease; sometimes so slight as to appear to be simple results of the anæmia. One would gather from the accounts they sometimes seem absent altogether, or so slight as to be not worth noting.

The facts which first drew my attention to this group of symptoms were those ascertained by the investigations I carried out between the years 1885—1888. The results of these, published in 1888, showed (1) that the blood change was essentially *hæmolytic;* (2) that this hæmolysis was originated and confined to the *portal area;* moreover (3) that this hæmolysis was of a *special character.* These facts pointed to the gastro-intestinal (portal) area as the seat of some special processes.

On *clinical grounds* alone there is no reason to attach to these symptoms—oral, gastric, and intestinal—any other significance or importance than was attached to them by all the earlier observers, and they include such notable clinicians and observers as Addison, Wilks, Biermer, Quincke, Immermann, Eichhorst, Pye-Smith, Bristowe, Bramwell, Coupland, and Mackenzie.

Addison made no mention of any such symptoms.

The occurrence of gastro-intestinal symptoms was noted by Biermer. He attached a double significance to them. If slight, they were effects of the anæmia. If severe, they were causes. "The most common cause was chronic diarrhœa, with or without gastric disturbance."

Following this teaching, almost all earlier observers attached a similar double importance to them. When severe, they were held to be themselves the cause of the disease; when insufficient to be accounted causes, they were regarded as effects (Eichhorst). This point I have brought out elsewhere (op. cit.).

And Dr. Pye-Smith, in his account of the disease in 1883, while referring to dyspeptic symptoms as common in the disease, evidently took a similar view of their im-

portance, since he defined the disease as "without any symptoms that could not be ascribed to the anæmia."

Significance.—The special significance I have been led —as *the result of my pathological studies*—to attach to these gastro-intestinal symptoms differs essentially from that above indicated. They do not, in my opinion, suggest the "gastro-intestinal origin," nor yet the "gastro-intestinal cause," nor yet the "gastro-intestinal nature" of the disease. Their significance is that they denote the *gastro-intestinal site of the infection causing the disease.* They derive their importance not from their severity, or their character, but from their existence at all in connection with this area.

As I have elsewhere shown, the symptoms of gastro-intestinal disturbance accompanying this anæmia include in the case of the *stomach* not only vomiting and diarrhœa, but almost every variety and degree of disturbance, *e. g.* indigestion, anorexia (sometimes alternating with ravenous appetite), nausea, sickness, pyrosis, salivation (rare), acidity, retching, vomiting, gastric pain, dilatation of the stomach with splashings, general discomfort over the stomach; in the case of the *intestine*, looseness of the bowels, diarrhœa, and colicky pains. And, as regards their frequency, an analysis I have made of a total of 279 recorded cases shows that the frequency of such symptoms is even greater than supposed, *mention* of gastric or intestinal symptoms being found in no fewer than 84 per cent. of cases.

The proportion might in my experience be increased up to 100 per cent., for they form a constant feature of every case *at some time or other*, although at times they may be in abeyance, or at most so slight in character as to be overlooked. As it happens, in the first case I observed and carefully studied, the absence of dyspeptic symptoms or gastric discomfort was a notable feature during the time he was under my observation. But they formed a prominent feature at one time before; and post

mortem I found evidences of subacute gastritis and atrophy of gastric glands.

Whether slight or severe they have an equal significance in my eyes. They stand to the disease in precisely the same relation as the intestinal symptoms stand to typhoid fever. They may be severe, as these latter may be; they may be moderate, as these latter may be; they may even be so much in abeyance as hardly to arrest attention at all, as the intestinal symptoms in typhoid fever may be. Yet all these variations are, in its case, as in the case of typhoid fever, compatible with the presence of lesions in the intestine—very obvious and definite in the case of typhoid fever; obscure and requiring to be sought for, but nevertheless there, in the case of pernicious anæmia.

As I have just said, the severity of this group of symptoms, indeed, varies much, both in different cases and in the same case at different times. This latter circumstance is of importance. A case may appear to be without symptoms of this kind at one time; yet at another later period, when the case is possibly not under observation, gastric or intestinal symptoms may be present. The important point about them in my judgment is, that they are not of sufficient severity or persistence to be themselves the cause of so grave and remarkable a form of anæmia, any more than the pain and discomfort of the throat or the slight fever can be adjudged to be the cause of the profound effects of diphtheria, or the gastric and intestinal symptoms in typhoid fever can be held accountable for the remarkable effects and course of that disease. They are mere symptoms. If very severe, *e. g.* vomiting, or diarrhœa, they of course, as in typhoid fever, add gravely to the exhaustion occasioned by the disease. Still, even then they are not the cause of the disease—pernicious anæmia,—they merely denote the site of the infection responsible for the disease.

In the case just described the gastric symptoms were prominent, and that, too, from an early stage of the

disease, as also the tongue symptoms, accompanied in their case by recognisable lesions which could be seen to come and go.

Pernicious Anæmia not a Gastro-intestinal Dyspepsia.

In this connection I may take occasion to correct an impression which prevails with certain writers with regard to the nature of these gastro-intestinal processes to which I attach importance. They are sometimes spoken of as if they were the result of some kind of gastro-intestinal dyspepsia.

I desire to draw attention to the fact that this is not my conception of the nature of the processes which give rise to the toxic substances responsible for the hæmolysis. They are the result of the special infection in the parts of the mucosa affected. Another misconception I may also take occasion to correct.

In the light of subsequent knowledge regarding the frequency of gastro-intestinal symptoms, I find it regarded by some as almost "natural" to conclude that the gastro-intestinal tract must be the seat of some special processes; that hence the portal area must "naturally" be the area specially affected by any increased hæmolysis produced by these "perverted intestinal processes;" and that consequently the liver must "naturally" show most evidence of this increased hæmolysis in the form of pigment.

I desire, however, to point out that the knowledge that thus seems "natural" was only arrived at after years of detailed work and experiment; that the order of progression of studies was precisely the reverse of that stated. It was, namely—

(1) Pigment changes in the liver.

(2) Portal site of hæmolysis.

(3) New significance attaching to gastro-intestinal processes.

In particular it took three years' work, involving many

experiments, to establish the fact that the portal area was the chief seat of hæmolysis, and thus to lay the pathological basis for the conclusion that the gastro-intestinal area was the site of the disease.

Infective nature.—The disease is not a special form of gastro-intestinal dyspepsia. It is the result of a definite infection of the mucosa, spreading from point to point, healing up in part, and then spreading to another. The special characters of the lesion can be best seen and studied, as in the present case, in the tongue—angry red patches, denuded of epithelium, on the dorsum of the tongue, followed by a smooth atrophied patch which persisted for weeks. And now that the disease is arrested, this patch has again become covered over with normal epithelium. But even now it shows from time to time signs of recurrence, denoting the deep-seated character of the infection *once it has taken root.*

4. Toxæmic Symptoms.

The class of symptoms I here designate "toxæmic" are those which, in my judgment, cannot be ascribed to the anæmia *per se*—*i. e.* to the actual poverty in corpuscles or in hæmoglobin; but denote rather the influence of other agencies of a *toxic character.* They all have one character in common—*periodicity.*

They really include many of the commonest and most characteristic features of the disease. That is to say, the intense feeling of illness and weakness which the patient experiences is not constant, but varies remarkably from time to time, sometimes even from day to day, independently of any recognisable changes in the blood sufficient to account for it.

The colour of the urine also changes periodically without any assignable cause.

The gastro-intestinal symptoms also display a no less marked periodicity. But the group of symptoms which I

desire to draw attention to by the special title "toxæmic," are those connected with the temperature and the nervous system—namely, *fever* and *nervous disturbances*. The symptoms connected with increased hæmolysis and gastro-intestinal irritation are evidences of more *local* disturbances—within the gastro-intestinal mucosa and the portal blood respectively. The fever and the nervous symptoms are evidences of more general and wide-spread disturbances.

Fever.—Fever is, in my experience, a notable feature of the disease, not so much from its character or its severity as from its existence at all. It is quite irregular in type, and very varying in degree. It may be, and often is, absent for considerable periods of time; but even in such cases it will be found that a slight rise of temperature at night—to between 99° and 100° F.—is the rule. Variations of a much more marked character occur from time to time, independently, apparently, of any cause. During these attacks all the other symptoms undergo exacerbation—namely, sense of illness and increase of weakness, increase of hæmolytic changes in the urine, occurrence of sickness or looseness of bowels —sometimes the one, sometimes the other predominating.

The fever is not always proportionate to the severity of the case, or the severity of the other characters of the disease. In other words, sometimes the *local*, at other times the *general* disturbances predominate. An interesting feature I have several times had occasion to observe is, that patients who have had a particularly sharp bout of high fever with general disturbance have often experienced a no less marked and sudden respite in the progress of their disease; whereas those who may be steadily losing ground may show only a slight rise of temperature.

These features are, I think, explained by the nature of the fever itself. It has been regarded as "anæmic" (Immermann), due to want of hæmoglobin, as "humoral" (Biermer).

My own view of it is that it is largely septic, and that all its characters find in this their fullest explanation, *e. g.* its irregularity, its slight degree when the disease is possibly advancing (denoting a total absence of power of reaction on the part of the body), or its occasional high degree, followed by rapid amelioration (denoting a sharp reaction on the part of the body).

Probably two factors co-operate to give it its irregular character: (1) the resistance of the body on the one hand; (2) the activity of the lesions on the alimentary mucosa and the toxic absorption on the other.

The gastro-intestinal irritation is due to the lesions themselves, the general toxic effects to the absorption. Even in health, with the blood normal, the effect of septic absorption on the temperature is variable enough, sometimes marked when the absorption is only slight, sometimes absent or slight when it is far greater.

In pernicious anæmia the blood is profoundly deteriorated, so that the wonder is that one ever gets a sharp reaction at all.

In the present case the fever was of the mild character (as will be seen in accompanying chart).

During the first five days its slight irregular character is well seen, varying from 97° to 99·6°; but during this time the blood had deteriorated by 3 per cent., and the urine was very dark, denoting active hæmolysis. The subsequent variations were connected with the serum injections, and it is to be noted how remarkably steady the temperature was at the period he was making rapid progress (adding 30 per cent. of corpuscles to his blood). After the last injection the temperature lost this steadiness somewhat, and it is interesting to note that the blood condition at this time remained stationary,—indeed, went slightly back.

Nervous Symptoms.

The other group of symptoms which I regard as specially toxic in origin are those connected with the

nervous system. They include not merely slighter effects, such as those I have mentioned, as intense sense of illness, weakness, utter exhaustion, but also more serious effects denoting actual affection of parts of the nervous system—sensory, motor, and trophic,—such as numbness, tingling, slight loss of power, actual paralysis.

The point of interest about them is that they occur at all; the degree of their intensity is a point of secondary importance.

In the present case they comprised numbness and tingling, and feeling of deadness in fingers, of which constant complaint was made (see history). Curiously enough they have proved the most persistent of all the symptoms. They still remain—after seven months—although they do not now give any trouble. The nature of the actual lesions associated with the severer forms of nervous affection in this disease is known to this Society from the very full account given by Dr. James Taylor in 1895.

The problem which this group of symptoms presents to me is the following (that they are toxic seems undoubted) :—Are they the effects of the special (hæmolytic) infection underlying the disease, or are they the effects of the antecedent and concurrent sepsis (oral and gastric), which in my experience is invariably associated with the disease?

For reasons I have elsewhere given ('Practitioner,' December, 1900), I regard them as largely of the latter character; and for this reason, that I have found precisely similar nervous effects connected with extreme oral sepsis, and unattended by any anæmia.

The fact, however, that these nervous effects, in slighter or more marked degree, are met with so often in this disease—in my experience in at least two thirds or more of the cases—suggests that they may also be due partly to the special (hæmolytic) poison of the disease itself.

Treatment.

The conclusions I have formed regarding the infective nature and special seat of the infective process have suggested new lines of treatment with regard, (1) first, to the possible prevention, and (2) possible arrest of the disease after it has declared itself.

From this point of view the important point is not so much the actual character of the organism concerned as the site of the original infection—the mouth, and the part played in this infection by antecedent and concurrent oral sepsis.

In their order of importance the following are the lines of treatment to be followed out, all of them exemplified in the present case.

1. *Oral antisepsis.*—Complete in its character, both with regard to diseased teeth, irrespective of any absence of pain or discomfort such teeth may be causing, and to the special lesions of the tongue.

2. *Gastric and intestinal antisepsis,* in effecting which removal of the oral sepsis is one of the most important measures to be carried out.

3. *Arsenical treatment,* of whose great value there cannot be a doubt.

For the improved prognosis with regard to the disease—the average duration being now in my experience some three years—the use of arsenic deserves, in my judgment, the credit. It is no less certain, however, in my experience, that arsenic alone cannot permanently arrest the disease.

The disease has, with very rare exceptions, hitherto always recurred, and eventually killed. This may possibly be due to the remarkable persistence of the infection, well exemplified in the present case by the recurrence of the lesions in the tongue. It may, however, be due to the fact that hitherto, the infective nature and oral site of the infection in the first instance not having been recog-

nised, the patient cured once of his disease by arsenic has been left with the local septic conditions which originally favoured the infection, and favour either renewed infection or extension of the old. How persistent the infection is! This, I would fain hope, has been the case; it forms the most favourable element in regard to the future prognosis of the disease, and the present case forms in that respect the most favourable one I have yet seen. Future experience alone can decide upon it.

If these measures combined serve to avert the disease permanently—and of the two I attach greatest importance to complete oral and gastric antisepsis—there will be no need for any other treatment. But if they do not, the only measure is the one I have recommended of (4) *antitoxic treatment*, with the hope of thereby antagonising the poisons within the blood responsible for the hæmolysis.

In the present case the treatment adopted was—

Period 1.—Oral and intestinal antisepsis—carried out continuously over a period of seven months.

Period 2.—Antitoxic serum (streptococcic).

Two injections of 10 c.c.
„ „ 5 c.c.

given in a period of three weeks.

Result:

Corpuscles	+ 40 per cent. (67 per cent.).
Hæmoglobin	+ 37 per cent. (72 per cent.).
Weight	+ 1 lb.

General health.—Greatly improved. Hæmolysis arrested (urine very pale).

Period 3 (six weeks).—Sent to the country; arsenic still withheld. As a tonic, ʒj of syrup of hypophosphites.

Result:

Corpuscles	— 3 per cent. (64 per cent.).
Hæmoglobin	+ 8 per cent. (80 per cent.).
Weight	+ 6 lbs.

General health.—Much better.

PERIOD 4 (six weeks).—Medicine liquor arsenicalis ♏2½ ter die.

Result :

Corpuscles	+ 16 per cent. (80 per cent.).
Hæmoglobin	+ 10 per cent. (90 per cent.).
Weight	+ 16 lbs.

General health.—Very good ; he looks in robust health.

PERIOD 5 (ten weeks).—Arsenic continued in ♏5 doses for six weeks, ♏2½ for four weeks.

Result :

Blood	+ 11 per cent. (91 per cent.).
Hæmoglobin	+ 14 per cent. (104 per cent.).
Weight as before.	

General health.—Robust, complexion high-coloured. Only symptom remaining is slight numbness at tips of fingers.

As regards the effects of the serum treatment, it was observed in this case, as in another case under my care, that the injection usually caused a distinct general reaction, lasting usually for forty-eight or sixty-four hours ; and several times, as already stated, there was a local reaction as well ; this latter, doubtless, due to some peculiarity of the serum employed.

Whether this reaction was connected with the character of the disease, or of the special serum used, it is impossible to state. But in view of its possible occurrence, it is, I think, advisable to begin with small doses (5 c.c.) ; and the precaution ought to be taken—as I have taken in the two cases I have had under my care—of (1) seeing that the temperature is not in an erratic condition at the time the injection is made ; (2) strengthening the heart's action by means of ammonia and digitalis.

As regards the probable scope of usefulness of this treatment, it is at present quite impossible to speak. As I have said, the object of it is not to replace the line of treatment hitherto employed—and up to a certain point

successfully employed—namely, by arsenic; nor is it to replace the new line of treatment by combined oral and intestinal antisepsis, which I. have recommended. To this latter I attach an even greater importance than to arsenical treatment, inasmuch as it aims at *the removal of the septic factor* associated with the origin of the disease—and of the infective lesions themselves.

It is intended to supplement both these lines of treatment if they fail to arrest the disease.

If both together fail to arrest the disease, this serum treatment appears to me to hold out prospect of benefit. And the case recorded—as also and still more the case recorded by Dr. Wm. Elder ('Lancet,' April, 1900), in which the blood condition rose from 16 per cent. of corpuscles and 24 per cent. of hæmoglobin, to 96 per cent. of corpuscles and 104 per cent. of hæmoglobin in forty-five days—certainly denotes that, carefully carried out, the serum has distinctly valuable therapeutic properties. In the present case the treatment was adopted early in the disease.

Should future experience show that complete antisepsis *plus* arsenic cannot arrest the disease, I should be disposed to carry out the serum treatment—not when the patient is at his worst, but in some period of partial arrest of the disease.

DISCUSSION.

Dr. C. REISSMANN.—I should like to ask the author whether there are any special changes in the blood by which we can actually diagnose the nature of the mischief. There are cases which clinically appear to be pernicious anæmia, but which when examined post mortem show distinctly other changes. I have met with two cases during the last two years which showed all the changes usually associated with pernicious anæmia: the red corpuscles were reduced to two millions, many were nucleated, there was poikilocytosis, etc., yet post mortem we found colloid cancer of the stomach which was not even suspected during life. The patient had complained of pain in the stomach, but there was nothing to suggest malignant disease. The changes in the blood met with in association with pernicious anæmia are known to occur in other diseases,—for instance, in leucocythæmia. There the diagnosis is usually easy because there are certain changes in the white corpuscles, but apart from that the blood presents the typical appearances of pernicious anæmia.

Mr. T. J. BOKENHAM.—I propose to say a few words in contribution to the discussion of this evening's subject, and to approach the question not from the strictly theoretical side but from a clinico-pathological standpoint. Ever since we became acquainted with the fact that highly poisonous substances are constantly formed in the digestive tract as a result of the normal vital processes, and with the additional fact that the intestine is a regular hotbed of micro-organisms, it has been a subject of wonder how it is constantly becoming the victim of auto-intoxication or auto-infection. It has seemed reasonable to suppose that the liver, placed as it is between the blood from the digestive tract and that of the general circulation, must play some prominent part in our system of defence. There has been a certain amount of experimental evidence in support of such a view. More than twenty years ago Sir Lauder Brunton drew attention ('Pract.,' 1880) to the work of Lussana, Schiff, and others, who found that both organic and inorganic poisons, when absorbed from the intestines or introduced by a mesenteric vein, were separated by the liver, being excreted with the bile into the duodenum, and thus being prevented from entering direct into the general circulation. He pointed out the importance of this function in relation to poisons formed in the intestine during digestion. Further experiment has since shown that in relation to certain poisons, *e. g.* strychnine, quinine, veratrine, and morphine, the liver has the power of converting them

into harmless substances or else of storing them up temporarily and then re-excreting them so slowly that no toxic effects become manifest. We thought it quite possible that a further study of these functions of the liver might not only throw additional light on the question of immunity from auto-intoxication, but also on the larger ones of bacterial immunity and antitoxin production. I will now state as shortly as possible some very interesting results arrived at in the course of an experimental investigation conducted on these lines, results which, I think, are entitled to a place in this discussion. Working with livers isolated from the general circulation, and passing through them a "serum" containing either diphtheria or coli toxin (the latter prepared by Salimbeni's method), I found that both these toxins become so altered by, or stored up in, the liver that the outcoming fluid is deprived of a great part of its toxicity. Using a weak solution of indol, and causing it to circulate in like manner for some time through the liver, I obtained a fluid which no longer gave the "nitroso-indol" reaction, nor was I able by distilling from the liver substance to obtain a distillate giving a typical indol reaction. Passing now from toxic substances to living cultures of micro-organisms, I would first allude to the observation of Wissokowitsch, that when bacteria were introduced into the general circulation they rapidly disappeared from the blood, and were then to be found in the liver, spleen, and red marrow. He thought that they were ultimately eliminated with the bile. Werigo, too, has made very similar observations, and attributes the chief part in the arrest of microbes circulating in the blood to the endothelial cells lining the hepatic capillaries. It seemed to me worth while to extend observations in this direction, and with this object I injected very slowly a bouillon culture of *B. coli* (a culture of vigorous growth, but scarcely marked virulence) into one of the mesenteric veins of a cat. After a few moments I made plate cultures from (*a*) a superficial vein, (*b*) the supra-hepatic veins, and (*c*) the bile-duct. From the first nothing grew; from the other cultures only a few colonies were obtained. After half an hour the animal was killed, and cultures were made from the blood and liver substance. A sparse culture was obtained from the latter only, although sections of the liver showed the presence of large numbers of bacilli. Under these conditions it seemed, therefore, that the liver had acted not only as a filter but also as a destroyer of bacteria. In another experiment I injected the culture into a systemic vein. Here, again, the blood proved sterile, while the liver gave a limited growth. These observations seem, therefore, to confirm and amplify those of my predecessors, and that it is the liver which plays a very important part in protecting the circulation, both from toxic matters and bacteria.

When I repeated these experiments with a highly virulent coli culture my results were somewhat different. Injection into a superficial vein was followed by a rapid disappearance of microbes from the blood, but they reappeared after an interval, and death ultimately took place from septicæmia. Examination of the liver of an animal killed soon after injection showed, however, the presence of very numerous bacilli, so that even in this case there seems to have been an effort on the part of the organ to protect the body from general infection. In another experiment I therefore used an animal which had received previous injections of coli serum. In this case the result was exactly the same as when I used a non-virulent culture in a normal animal, as I proved both by the microscope and by culture. It looks as if the action of the coli serum had been to stimulate and strengthen the normal action of the endothelium of the hepatic capillaries. Perhaps at no distant period we may make use clinically of such a probable action of a specific serum in the treatment of certain auto-intoxications or auto-infections from the digestive tract. Finally, I would recall a suggestion which has often been made by Sir Lauder Brunton, that under certain circumstances the liver may so act as to remove certain protective substances from the blood, rendering the body even more than normally susceptible. We know how often a "cold" follows the use of calomel, although that drug is of undoubted benefit in removing the toxic substances which produce "biliousness." I am aware that another theory as to this susceptibility to cold after calomel is generally accepted, but I would submit that this "anti-antitoxic" theory is at least another possible explanation of its action.

Dr. S. COUPLAND.—We ought really to express the feeling which must animate us all of the extreme value of the service which the author has rendered to medicine by his patient and careful investigations into what has hitherto been regarded as a very mysterious malady. He has pretty well lifted the veil, and we now have a very fair notion of what pernicious anæmia really is. If I followed him correctly, the conclusion he seems to have arrived at is that pernicious anæmia is a hæmolytic disease excited by a specific poison which operates through the portal system, and that this specific poison only acts when the way is prepared for it by septic infection of the alimentary tract. It only remains for him to demonstrate the true nature of the specific poison, and, perhaps, to isolate the bacterium which is responsible for this mischief. That there must be a special poison (whether bacterial or not is immaterial) must surely be evident when we consider how rare pernicious anæmia is, and how common, alas! is oral sepsis. Dental surgeons could produce thousands of cases of this condition of the teeth and mouth for one of pernicious anæmia which a physician may show.

That, I imagine, is the position to which Dr. Hunter has now brought us.

Dr. SAVILL.—As regards the clinical aspect of pernicious anæmia, I think that we might with advantage reconsider the question of its position in nosology. Among my out-patients at the Hospital for Nervous Diseases quite three quarters come complaining of symptoms which we regard as neurasthenic, and a large number of these are of a vaso-motor kind. I have not taken the pains to observe with great accuracy whether they have had anæmia or not, but my impression is that a very large number of these cases were anæmic, and many presented the earthy complexion so common in dyspepsia, from which many of them suffer also. Their urine might be examined for hæmolysis, and thus possibly they might be brought within the category of this disease. In a word, I am inclined to think that the condition under consideration is by no means as rare as it was formerly thought to be. Of course one has always looked upon pernicious anæmia, prior to the researches of Dr. Hunter and others, as a severe and almost necessarily fatal disease, occurring chiefly in old men, but I see no reason why the cases I have referred to should not be of the same nature, only slighter in degree. The commonest cause of these neurasthenic cases is undoubtedly dental defect of some kind; a large number of them have suppuration going on in the mouth, and the cure of these cases rests largely with the dentist. I think, therefore, there is a very large field which might profitably be investigated from this point of view.

Mr. A. BARKER.—The investigations which the author has brought before us to-night have a great interest for surgeons as well as for physicians. First I would thank him for having drawn my attention to a very important subject, viz. the examination of the state of the mouth and tongue in certain conditions. Honestly, I feel almost ashamed, for I am obliged to say that I saw that specimen to-night for the first time, though it was taken from one of my patients. I was not aware that during life he had anything wrong with his mouth. He had suffered from a very serious gastro-intestinal condition, and he was nearly moribund when Dr. Hunter saw him first. In future, I shall certainly not allow any case like this one to pass through my hands without most careful examination of the mouth, and examining it in a way it has not hitherto been examined. He has shown us how very scrupulous we should be in certifying the fact that the condition of the mouth will produce profound anæmia and depression of vital energy, though in surgical cases that has been known to us for many years; indeed, for some years past we have been accustomed to endeavour to treat all cases in which we were going to operate upon the mouth in the direction of antisepsis, but I do not think we have realised how

the state of the mouth can contribute to the production of specific diseases of the intestine and stomach. The question, indeed, appears to me to be as interesting to surgeons as to physicians. In that case of mine, I believe the author was led to search in the man's mouth and frontal sinuses by a process of reasoning based upon the condition of the liver, spleen, stomach, and intestine, a thing which it had not occurred to us to do.

Dr. W. HUNTER —I am certainly indebted to Mr. Barker for one of the most valuable proofs I have had in my investigation of these cases. His case came within a month of my first article on this matter, and it was my first post-mortem. I think that one of his colleagues proceeded to examine the mouth. The front teeth were beautiful, but the back teeth were in the condition I have described. There was no obvious sign of trouble, but very marked pallor. Then I cut out the jaw and found an alveolar abscess. I wanted to examine the eyes, and on taking off the orbital plate a lot of pus oozed out. Of this condition of sepsis there was no suspicion during life. My conclusions are based on seven cases, now raised to ten, which all show clearly the connection between the morbid phenomena and the symptoms. I am very indebted to Dr. Coupland. In my paper I have thought it necessary to apologise for having ventured to come to such a different conclusion respecting pernicious anæmia from my predecessors, Dr. Coupland, whose great lectures on anæmia formed for a long time the basis of our knowledge, Sir W. Broadbent, and others. If I attached importance to any group of features to which they did not attach importance, it is for the reason that my pathological studies had given a basis to this gastro-intestinal condition which did not exist before. No one can attach to the condition of the mouth or tongue such as I have described any importance whatever on purely clinical grounds. Since this view has been brought forward, the term "gastro-intestinal" has been used in quite an unwarrantable manner, as if, indeed, pernicious anæmia were a mere gastro-intestinal disturbance. The condition of the gastro-intestinal tract is not the cause of the anæmia, but the result of the lesions which produce the anæmia, *i. e.* they tend to pernicious anæmia in the same relation as the lesions of typhoid fever or diphtheria do to the disease, but in no other way. I repudiate having formulated any gastro-intestinal hypothesis of the production of pernicious anæmia. The diagnosis of this disease is not to be based upon the blood-changes alone, but upon the blood-changes in association with four groups of clinical features which are as definite and as constant as that in connection with any other disease with which we are acquainted, viz. (1) anæmia, (2) changes in the character of the urine, (3) gastro-intestinal symptoms, and (4) general

effects, fever, etc., showing the effects of toxic absorption; and in connection with this there are a group of nervous lesions. I should be quite willing to exclude any case in which these four groups of symptoms were not present. A few months ago my attention was called to a case in which there was a history of suppuration of the jaws, and which had been diagnosed as pernicious anæmia. There was even a history of numbness and tingling of the fingers, yet, on examining that patient, the urine was perfectly pale and contained a slight trace of albumen. That patient died two months later from uræmic coma. In the paper I have shown that the streptococcus is only an associated organism, and I attach importance to it merely because it ought not to be there. I have shown that the streptococcus is not hæmolytic, and so far I know nothing of the nature of the special organism involved. It is a difficult task to isolate a particular organism in the mouth and stomach, but now we have traced the lesion back to the tongue perhaps we may be able to do something more.