

T H E S I S

for the

DEGREE OF DOCTOR OF MEDICINE (M.D.)

presented by

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Ruchill, City of Glasgow Fever Hospital,

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S U B J E C T

"A Clinical Study of the Presence and Sig-
nificance of the Indoxyl Salts in the
Urines of Patients suffering from the
Acute Infectious Diseases"

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INTRODUCTION

The investigations on which these observations are based were carried out in the City of Glasgow Fever Hospital, Ruchill, during a period extending from October, 1909, to March, 1910.

Although attention has been given by Simon and others to the presence of indigo in the urine, principally in diseases of the intestinal tract, such as gastritis (acute and chronic), malignant disease of the stomach, gastric and duodenal ulcer, yet so far as I have been able to ascertain, no detailed investigation has been carried out in the acute infectious diseases.

The particular objects of the present investigation were:-

- 1 To collate the relationship of the amount of indigo present in the urine with the clinical course of the disease.
- 2 To consider its value as an aid to prognosis.
- 3 To examine as to whether the amount of indigo in the urine was solely related to intestinal disturbance.

The urines were examined chemically; and in all, over five hundred (500) cases were examined daily (with very few exceptions) throughout the course of the illness, the residence in Hospital varying from a fortnight in some measles cases to eight weeks and upwards in Scarlet and Enteric Fever: fresh specimens were examined. An account of the investigation is arranged in

the following order:-

- I Method of Examination employed
 - II Cause of Indicanuria
 - III Relation of Indicanuria to various features of disease
 - IV Classification of Cases
 - V Conclusions
 - VI References and Bibliography.
-



I METHOD OF EXAMINATION EMPLOYED

Various qualitative and quantitative methods have been proposed for the detection of indigo in the urine. The chief quantitative methods are those of Bonma and Wang, the former estimating the indican as indigo blue after oxidation with Ferric Chloride, the latter estimating it as indigo red after treating the urine with Isatin.

The best known qualitative methods are those of Jaffe, Obermayer, Amann, Richardson and Senator, differing for the most part from each other in the oxidising agent used: Obermayer and Amann claiming that by the use of Ferric Chloride and Sodium Pyrosulphate respectively, the danger of excessive oxidation is averted.

In a research such as this where large numbers of urines have to be examined daily, some method, both qualitative and roughly quantitative, was necessary, and after numerous trials of the above-named methods, a modification of Jaffe was adopted, which, after a little practice, appeared to give fair comparative results readily estimable by the eye. The amount of indigo indicated by this method was checked by the quantitative methods of Bonma and Wang. With regard to these latter, I have made no attempt to consider their relative values: both seem from the criticisms to which they have been subjected to be not free from fallacy, though Bonma's method is probably the more satisfactory one. The defect of the method of Wang seems to be that if much indigo-red is formed during the process of ox-

idation, the resulting analysis must give a considerable deficiency in the amount of indoxyl present in the urine.

A. QUANTITATIVE METHODS employed in the examination
for the presence of indigo

A brief description of both methods is as follows:-

(1) Bouma's method¹

- (a) Add 1 volume of a 20% solution of acetate of lead to 10 volumes of the specimen of urine
- (b) Filter
- (c) To the clear filtrate add an equal quantity of a solution of Isatin, made by dissolving 20 milligrams of Isatin in 1 litre of concentrated Hydrochloric Acid
- (d) Heat for quarter of an hour in a boiling water bath
- (e) Cool.
- (f) Shake up with chloroform in a separator: this is repeated until the chloroform is clear.
- (g) Run off the Chloroform
- (h) Evaporate the Chloroform to dryness
- (i) Dry the precipitate for two hours in a hot air bath
- (j) Extract the precipitate with hot water to get rid of any remaining Isatin
- (k) Dissolve the dry precipitate with strong Sulphuric Acid
- (l) Add to 100 c.c. distilled water
- (m) Titrate with 1 in 10,000 Chameleon

(2) Wang's method²

- (a) Take 25 c.c. to 300 c.c. of urine (according to the amount of indigo in the urine
- (b) Add 25 c.c. to 50 c.c. of a 20% solution of Acetate of Lead

- (c) Filter
- (d) To the filtrate add an equal volume of Obermayer's reagent made by dissolving two grams of Ferric Chloride in 1 litre of strong Hydrochloric Acid
- (e) Shake the mixture with Chloroform in a separator, repeating until the Chloroform is quite clear
- (f) Run off the Chloroform
- (g) Distil off the Chloroform and dry the precipitate on a water bath for some minutes
- (h) Add 3 c.c. of strong Sulphuric Acid and shake until the indigo is all dissolved
- (i) Allow this to stand for 24 hours
- (j) Add 100 c.c. of water (the sulphuric acid is added carefully to the water to prevent the formation of indigo crystals)
- (k) Titrate with 1 in 20,000 Potassium Permanganate solution

(3) A third method (described by Maillard³) did not seem so satisfactory and was not tried. It is a colour method "consistant a nitrer les couleurs indigotiques et a doser colorimetriquement l'acide pierique forme. "

B. QUALITATIVE METHOD employed for the examination of the presence of indigo in the urine

The qualitative method adopted was to add an equal quantity of concentrated Hydrochloric acid to the sample of urine as recommended in all the processes in order to liberate the free indoxyl: three (3) drops of a solution of equal quantities of water and Liquor Calcis Chlorinata B.P. were then added, with the result that a band of indigo formed at the junction of the fluids - the upper part of the fluid was clear (un-

less albumin was present, in which case there was a white turbidity varying in density according to the amount present), and then came the zone of indigo. After some experimentation, a rough scale of $\frac{1}{2}$, 1, 2, 3, 4, 5 etc., was arranged according to the density of the indigo ring (see Diagram). If a certain depth of opacity was obtained, the urine was diluted and the test done over again. Twenty-one cases were examined at a time, the reagents being added and the respective rings examined in a definite order, this being necessary owing to a tendency of the ring to become intensified on standing. The density of each ring was noted $1\frac{1}{2}$ minutes after the addition of the oxidising agent.

This test was adopted in preference to others, in as much as it provided a zone where the oxidation into indigo was complete with a contrast layer of clear fluid containing oxidised indigo above, a method much preferable to attempting to bring the whole specimen of urine to a maximum hue by gradually adding an oxidising agent. Hyper-oxidation is in this way so easy that the intensity of colour produced is almost invariably considerably in defect of that observed when the ring test is used.

In order to test the relative value of the rings used in the qualitative method, a number of examinations were conducted by the quantitative method of Bouma. Specimens of urine were taken containing an amount of indigo corresponding to 1, 2, 3, 4 and three examples of each were examined. In the description of his method, Bouma gives no indication as to the point at which he concluded his titration with Chameleon, so the idea was formed of utilizing the well-known bands of potassium permanganate as recognized by the Spectro-

scope. To my own eye, I found that 3 c.c. of 1 in 10,000 Chameleon in 100 c.c. of water gave the distinctive bands, so in noting the number of cubic centimetres of Chameleon required for titration, this amount (3 c.c.) was subtracted from the total amount used.

From the subjoined table, it will be seen that the rings represent fairly constant amounts, and that a specimen containing "4" probably contains twice as much indigo as another specimen whose ring corresponds to "2" (see Diagram).

	No. of ring			
	1	2	3	4
No. of c.c.'s of 1 in 10,000 Permang. Pot. sol. used in titrating 1st specimen	35.1	41.6	53.6	94.4
No. of c.c.'s of 1 in 10,000 Permang. Pot. sol. used in titrating 2nd specimen	37.4	39.2	54.8	91.1
No. of c.c.'s of 1 in 10,000 Permang. Pot. sol. used in titrating 3rd specimen	32.3	43.8	50.4	92.6

II CAUSE OF INDICANURIA

Although it was formerly thought that indican was also formed within the tissues of the body in the absence of putrefactive organisms, it is now considered to be a product of the intestinal putrefaction of proteids. In the process Indol is first formed, is absorbed in the intestine and oxidised in the blood, forming Indoxyl, Potassium Indoxyl Sulphate, and finally Indoxyl Sulphuric Acid or Indican.

Subsequent researches have demonstrated the fact that micro-organisms are always concerned in the production of indican⁴, and this is borne out by the fact that Baumann⁵ absolutely disinfected the intestinal tract of a dog by means of calomel, and observed that all traces of indican disappeared: also that Senator⁶ found that indican does not occur in the urines of newly born infants that have not as yet received nourishment.

That an excessive indicanuria may also be caused by albuminous putrefaction occurring within the body (though this be due to micro-organisms), will be shewn by observations noted in the cases of Adenitis that went on to suppuration, otorrhoea etc.

III RELATION OF INDICANURIA TO VARIOUS FEATURES OF DISEASE

At a subsequent stage of this paper a description will be found of the amount of indigo present in the urines of patients suffering from the various diseases investigated. The cases that pursued a normal course have been grouped according to the severity of the disease as indicated by the temperature where this was possible (for an example see "Measles" p. 25): Diphtheria proved an exception, and in this disease the severity was judged by the opinion of the medical officer of the ward and by the amount of antitoxin the patient received.

Each disease is considered separately and the amount of indigo present during the course of the disease shewn: a short description of the cases that suffered from complications is also given and the relationship of the amount of indigo to these indicated.

From the results observed, the excess of indigo has been correlated to:-

- (a) The Nature of the disease and its type.
- (b) The temperature
- (c) The Nature of the complication
- (d) The issue of the disease

(a) THE NATURE OF THE DISEASE AND ITS TYPE

The most striking point noticed on examining the urines of patients recently admitted suffering from the acute fevers is the excessive amount of indigo.

The disease in which this is most markedly present is Measles. Enteric Fever follows next, while Diphtheria, Scarlet Fever, Typhus Fever and Erysipelas shew a progressive diminution in that order. With regard to measles, the average amount present was higher in the severe and medium groups than in any other disease, while in the mild group the amount was only equalled by enteric fever (see p. 25). This excess was observed in 114 cases, a larger number than was examined in any other disease. The maximum amount of indigo that was estimated was "8", and this frequently occurred, while in other diseases it was only occasionally noted.

The cases of enteric fever shewed an excess of indigo next in amount to those of measles. Among the cases in the severe group, the average was higher than in any other disease except measles, while in the medium and mild groups it was very nearly the same as that seen in scarlet fever, diphtheria and erysipelas. The maximum present in any individual case was "6" - an amount seen in scarlet fever and diphtheria but exceeded only by measles.

Scarlet fever has a similar average in all its three groups, but the severe cases shew a greater variation, that group giving a considerably higher range than the other two.

The cases of typhus fever are all contained in one group - the severe - and though fewer in number they shew a low average ("2") similar to scarlet fever and erysipelas and exceeded by measles, enteric fever and diphtheria. The maximum amount ("4") was not so high as seen in other severe groups.

Diphtheria occupies a position after measles and

enteric fever, and above scarlet fever, typhus fever and erysipelas. The maximum amount seen in individual cases was the same in all three groups, viz., "6", but the average amount was in accordance with the severity of the attack.

Erysipelas shows the lowest average over all the cases. In the severe group it was the same as in scarlet fever and typhus fever ("2") and in the medium and mild groups the average was below that seen in any of the other diseases.

From the above short description of the average amount of indigo present in the various diseases, it will be seen that measles and enteric fever shew a considerably higher percentage than the other acute infections. The only reference to the presence of indigo in the urines of patients suffering from infectious disease that I have been able to obtain is by Churton⁷. He states that "he found indican present in typhoid and other fevers, and in twelve cases of the former he found it in all its stages." In a second paper⁸ the same author said, "that he had demonstrated its absence in some cases of typhoid, prolonged constipation and strangulated hernia, and that it was therefore not correct to say that disease of any kind involving the intestine was attended by indicanuria." His results are merely qualitative and he makes no attempt to express the amount in a quantitative manner.

In my series of fifty-three cases suffering from enteric fever, whose urines were examined throughout their stay in Hospital, indigo was found to be always present in greater or lesser amount: in fact it was the exception not to find indigo in any urine examined, as this occurred on only twenty-seven (27) occasions, though

CHART I - Showing the association between Pyrexia and excessive Induration.

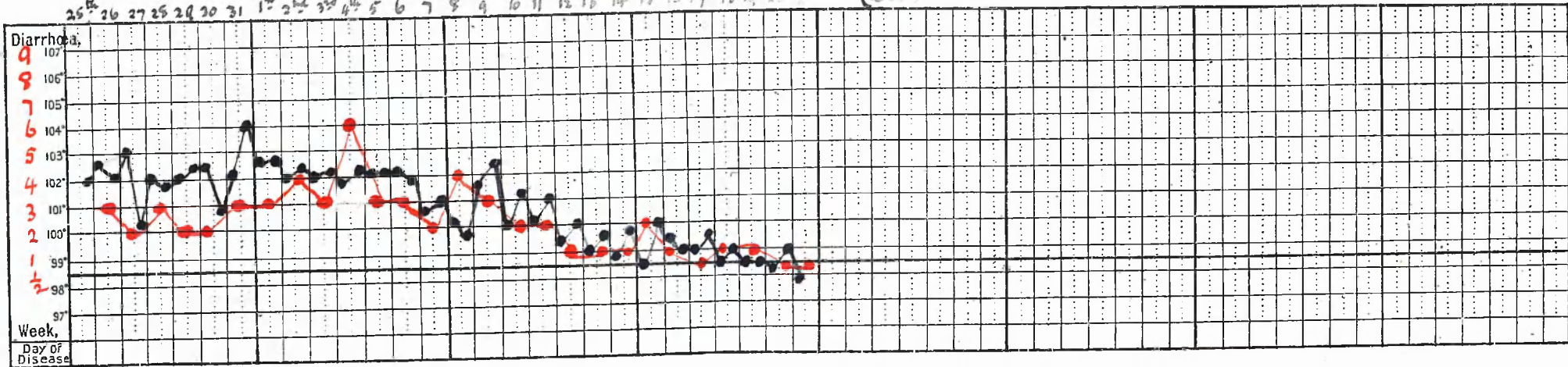
December 1909 January 1910

25th 26 27 28 29 30 31 1st 2nd 3rd 4th 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21st (etc.)

Journal Reference,
M^{rs} Myers
Sex, Female Age, 28 years

Result,
Recovery

Complications,



Remarks,

Black ink represents morning and evening temperature
In Red Ink, the number at the side represents the density of the ring while the red dot represents the density each wing.

the test was performed over 20,000 times.

From the etiology of indicanuria already detailed, one might conclude that the reason for their being an excess of indigo in the urines of patients suffering from enteric fever is because it is primarily a disease of the intestinal tract, which is therefore "thrown out of gear" by the infection: furthermore, there is present an excessive number of micro-organisms by whose agency putrefactive decomposition occurs. In the case of measles, however, an explanation of the increased indicanuria may be that the average age of the patient is much lower and that a younger child is more prone to have its digestive tract upset than one of a more advanced age. This may be due to anachlorhydria or hyperchlorhydria, as from Simon's own observations he came to the conclusion that an increased degree of intestinal putrefaction was largely regulated by the acidity of the gastric juice.

In typhus fever, diphtheria, scarlet fever and erysipelas, the smaller amount of indigo present as compared with measles and enteric fever might perhaps be ascribed to the facts that in these diseases there is no specific intestinal lesion, that the average age was higher and therefore the patient was not so liable to be upset by the infection.

(b) THE TEMPERATURE

That an association exists between hyperaemia and an excess of indican, abundant evidence is forthcoming (for example, see Chart I). This is particularly the case when the temperature is raised above 100° F., though in a few instances the first specimen of urine

contained only a normal quantity of indigo, while on the following day the specimen shewed the excess that might have been expected from the beginning. When it is considered that the indoxyl has to be formed, absorbed and then excreted before appearing in the urine, these exceptions are fully explained. Below 100° F. the amount of indigo present was usually raised to a slight extent, though in quite a number of cases it remained normal.

The reason for this relationship between the amount of indican present and the temperature may be explained by the fact that the amount of bile, gastric juice and pancreatic juice secreted during a period of pyrexia is diminished. Sahli⁹ states that if the duct of the pancreas is occluded the amount of indigo in the urine is diminished, while Simon¹⁰ points out that a subnormal amount of free Hydrochloric acid calls forth an increased degree of intestinal putrefaction and therefore an increased formation of indol with a corresponding excess of indigo, both observations favouring the assumption that there is a relationship between the amount of indigo present and the pyrexia. As it is well known that pyrexia is associated with diminished secretion from all the secreting glands, this is just what one would expect. The only exceptions were from among patients suffering from erysipelas, but in this disease there is much less interference with the digestive functions than in other diseases, the patients are older, and in addition, from the moment of admission, they have their bowels well regulated.

(c) RELATION OF INDICANURIA TO COMPLICATIONS

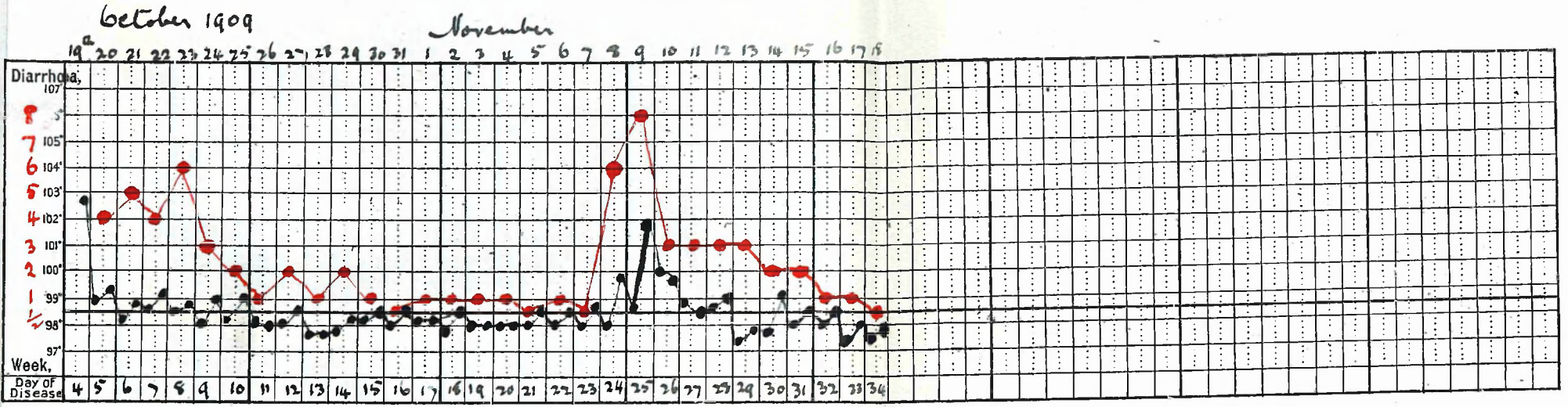
From the outset, one of the objects of this investigation was to ascertain if there was any relationship between the onset of a complication occurring during the course of an acute fever and an excess of indigo in the urine.

Among the cases of the various infectious diseases examined, complications frequently occurred and therefore a good opportunity was obtained of investigating this point. Only complications actually occurring during residence are reported. They have all been grouped together and examined in the following order:-

- 1 Simple Adenitis
- 2 Inflammatory conditions that have gone on to supuration
- 3 Otorrhoea
- 4 Albuminuria and Nephritis
- 5 Secondary sore throat
- 6 Bronchitis and Pneumonia
- 7 Pleurisy
- 8 Rheumatism
- 9 Diarrhoea
- 10 Constipation
- 11 Phthisis
- 12 Relapse occurring in erysipelas
- 13 Relapse " " enteric fever
- 14 Haemorrhage " " " "
- 15 Perforation " " " "

Chart II showing the effect of Adenitis. (Case 52)

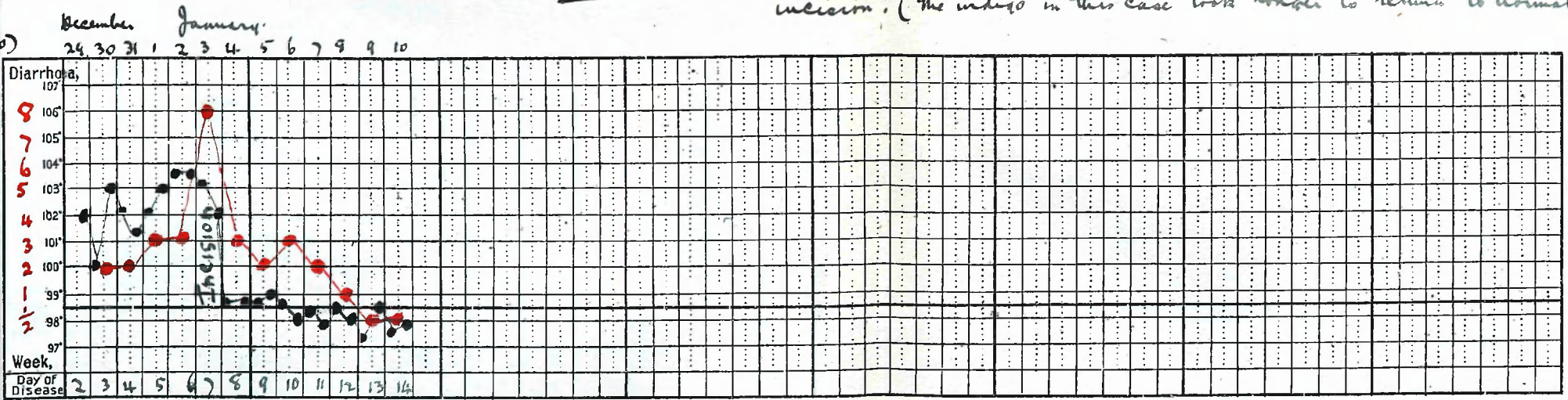
Journal Reference,
M. I.
Sex, female Age, 4 yrs.



Result,
Recovery
Complications,
Adenitis
on the 24th day
of illness.
Remarks,

Chart III showing the increase in the amount of indigo with suppuration and the effect of an incision. (The indigo in this case took longer to return to normal than any other)

Journal Reference,
G. M. C. (Case 50)
Sex, male Age, 7 yrs.



Result,
Recovery.
Complications,
Adenitis with
Suppuration.
Remarks,

1 Simple Adenitis

Fourteen (14) cases of this complication occurred during the course of these observations. In each case elevation of temperature to a greater or lesser extent occurred, and a definite increase in the amount of indigo noted, sometimes reaching as high as "8" as in Case 52 and never below "2" (see Chart II). The presence of pyrexia occurred synchronously with the clinical evidence of glandular enlargement, but the day on which the increase in the amount of indigo was observed varied in different patients. In one case it occurred three (3) days before the enlarged glands could be palpated, in two cases two (2) days, in three cases the day before, while in the remaining eight cases the increase occurred on the same day as the elevation of temperature. As the latter subsided the indigo returned to normal.

2 Inflammatory Conditions that have gone on to Suppuration with Formation of Abscesses

Inflammation proceeding to suppuration occurred in seven patients whose urines were being examined. An increase in the amount of indigo was noted in all the cases for three days previous to the presence of pus being detected, in one case to as high as "6" as in Case 50 (see Chart III), but on the whole averaging "4". More striking, however, was the diminution in the amount of indigo during the twenty-four hours succeeding evacuation of the abscess: in four of the cases it had returned to normal next day, in two cases it was normal

Chart IV showing the effect of blorrhoea.

Journal Reference,

S.C. (Case 48)

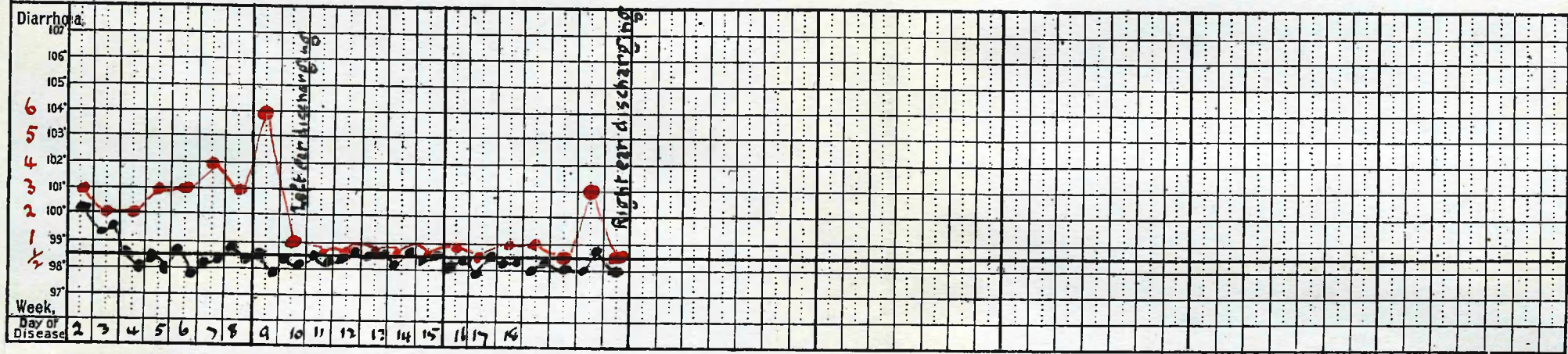
Sex, female Age, 9 yrs.

Result,

Recovery

Complications,

Blorrhoea



Remarks,

on the second day and in only one case was it delayed as long as the third day.

Sajou¹¹ states that indicanuria occurs in cases of decomposition of pus such as empyema, gangrene of the lung etc. but Beckman¹² considers that there is no causal relationship between indicanuria and suppuration, and that the increase of the former is of no value in revealing a hidden abscess. In the light of such statements, my own results described above combined with those described in the succeeding paragraph on Otorrhoea, and more particularly case 29 (see Chart XIII), who developed a pelvic abscess, are significant. They entirely agree with Sajon, but I would go further and say that there is always an excess of indigo during the process of suppuration - furthermore that it rapidly diminishes when the pus is evacuated.

3 Otorrhoea

This complication occurred in seven cases and the results observed give further evidence of the relationship existing between the presence of pus and excess of indigo in the urine. In one case the increase was noted five days before the discharge appeared, in two cases four days before, in one case two days before, and in two cases the day before: it returned to normal the day after the appearance of the discharge in three cases, two days after in two cases, and in one case it was delayed as long as the fourth day. Case 98 (not included among the above) is particularly interesting (see Chart IV). For five days before the left ear commenced to discharge, the indigo varied between "3" and "6" and on the appearance of the discharge it returned to normal, where it remained for ten days: the indigo

Chart V - showing index returning to normal after the disappearance of the albumin

Journal Reference,
K. O'C (case I)
Sex, female Age, 5 yrs.

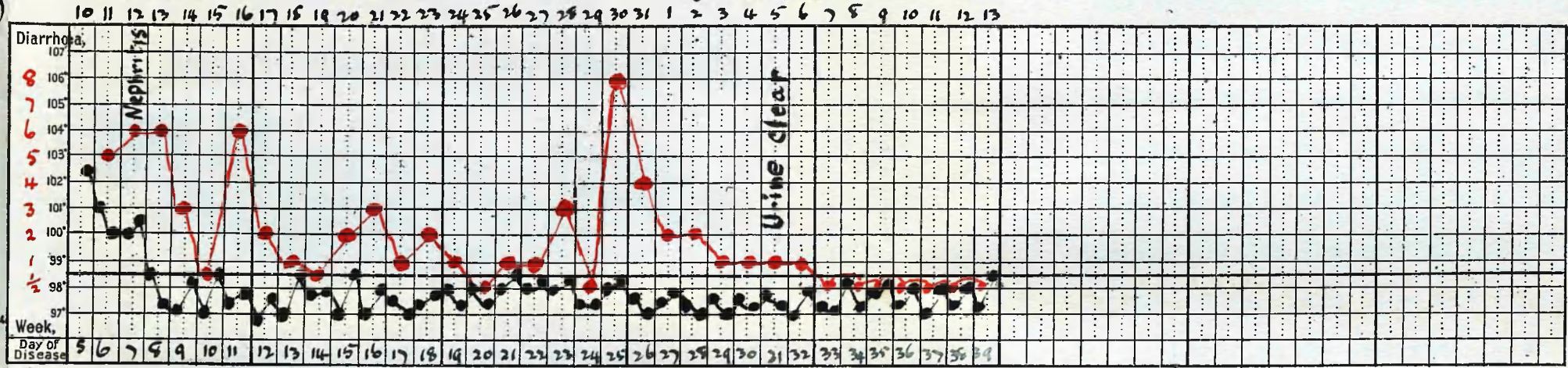
December 1909

January 1910

Result,

Complications,

Nephritis
on 7th day of disease
Urine clear on 31st
day of disease.
Remarks,



then suddenly increased to "3" but returned to normal the following morning, when it was found that the right ear had commenced to discharge.

4 Nephritis and Albuminuria

Acute Nephritis occurred as a complication in only three of the cases who were under observation. In one of these the onset was accompanied by an increase in the amount of indigo to "8", in the second to "6" (see Chart V), and in the third case to " $1\frac{1}{2}$ ". In two of the cases the indigo disappeared when the urine became normal, but in the third case, though the albumin persisted for two months longer, the indigo returned to normal after four days and remained there.

Albuminuria occurred in seven cases distinct from the above. With the development of this complication an increase in the amount of indigo to "3" was noted in all the cases except one: in four, it occurred at the onset of the complication, in one two days before, and in the remaining case the day before the albumin was detected in the urine. The return of the indigo to normal and the disappearance of the albumin coincided in four of the cases: in one, the indigo returned to normal the day after and in one case three days before the urine became clear.

Daremborg and Perroy¹³ in a series of observations found, that if a definite amount of albumin was present in the urine, 20% contained an excess of indigo, while if only a trace of albumin was present 11% contained an excess of indigo. They also state that in eighteen urines which contained an excess of indigo ten were albuminurics with a definite amount of albumin, seven

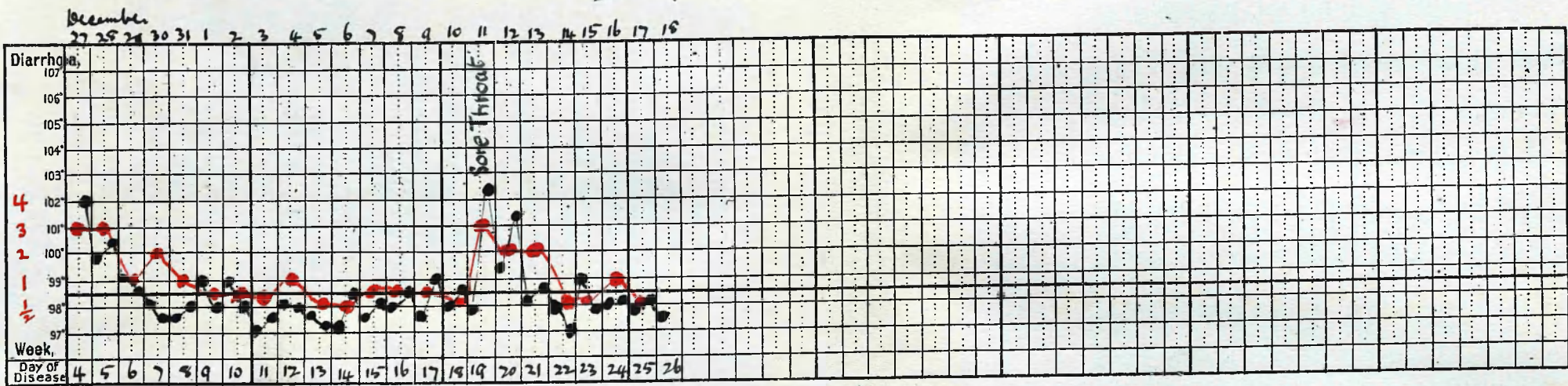
Chart VI • showing increase of index with Secondary Sore Throat.

Journal Reference,
 A. M. L.
 Sex, female Age, 29 yrs.

Result,

Complications,
 Secondary
 Sore Throat.

Remarks,



shewed a trace while only one indigotic urine shewed no trace of albumin.

The ten cases I have described bear out what Daremberg and Perroy have observed in the first part of their paper, though my percentage is very much higher, being 80% as against 20%. This may be accounted for by the fact that they give no indication as to what they regard "excess of indigo". With the second part of their statement my observations do not agree, as of fifty-six specimens of urine which contained an excess of indigo only eleven were found to contain albumin, giving a percentage of 20 as against 55. Their results are summed up as follows:-

"The renal disturbance indicated by a slight amount of albumin is not sufficient to produce an excess of indigo. If you get an excess of the latter examine the urine for albumin (the remainder of their conclusions is best described in their own words) et alors, nous sommes bien obligés de détruire la légende de l'origine intestinale des dérivés de l'indol et du scatol, et de regarder l'indol et le scatol, non pas comme des générateurs, mais bien comme des noyaux résiduels provenant comme le phénol de coups chimiques d'une constitution beaucoup plus compliquée.

5 Secondary Sore Throat

In the five cases which developed this complication an increase in the amount of indigo was observed at the same time as the elevation of temperature occurred (see Chart VI), and it varied in amount according to the degree of pyrexia. Its significance is therefore dealt with under "Relation to Temperature".

Chart VII - showing excess of indigo during an attack of Bronchitis (Case 12)

Journal Reference,
M.S. (Case 12)
Sex, female Age, 5 yrs.

Result,
Recovery.
Complications,
Bronchitis

Remarks,

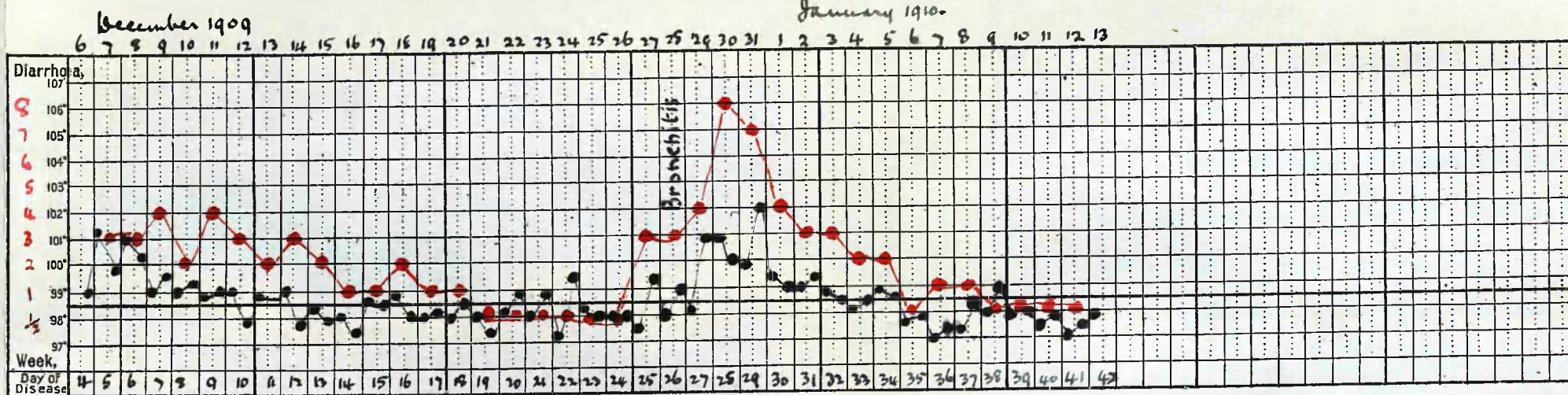


Chart VIII showing increase of indigo during an attack of Pleurisy and its return to normal after the chest was aspirated.

Journal Reference,
H.C (Case 45)
Sex, female Age, 15 yrs.

Result,
Complications,
Pleurisy with Effusion

Remarks,

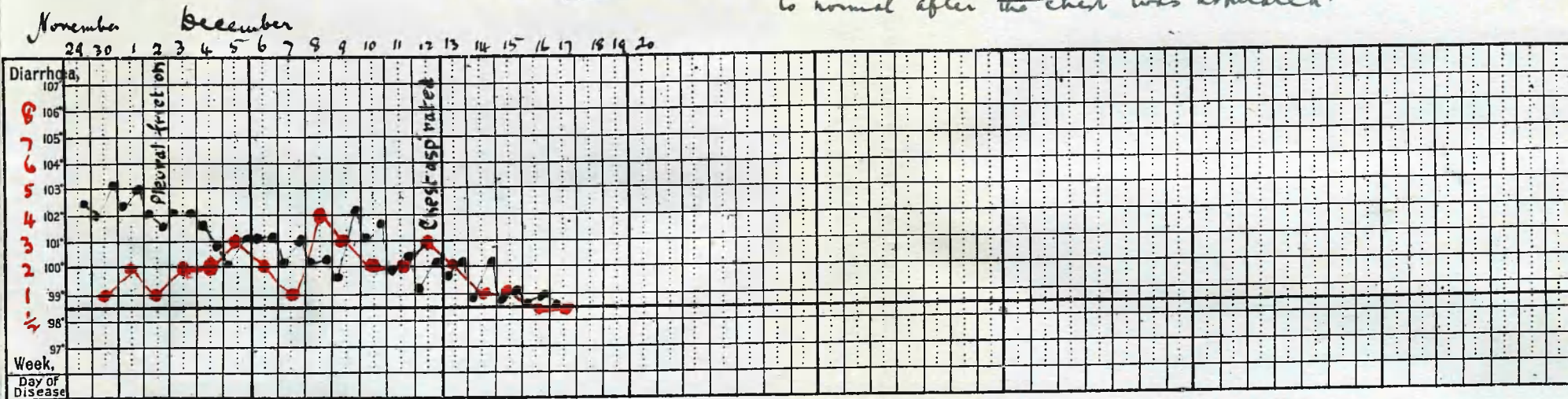
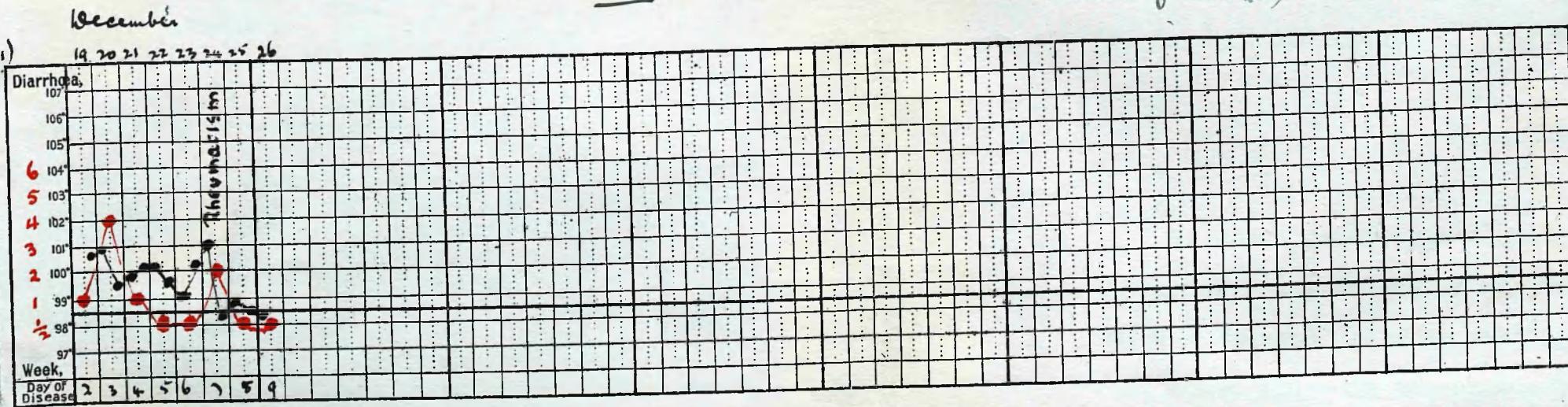


Chart IX (showing onset of Rheumatism corresponding with increase in the amount of indigo)

Journal Reference,
M.M.C (Case 61)
Sex, female Age,

Result,
Complications,
Rheumatism

Remarks,



6 Bronchitis and Pneumonia

Four cases developed Bronchitis and all shewed a marked excess of indigo at the onset of the complication, the lowest noted being "6" while the highest was "10". It remained high throughout the complication and gradually fell as the temperature returned to normal (see Chart VII). The same relationship between indicanuria and temperature was noted in two cases of broncho-pneumonia (Nos. 60 and 97). Case 88 developed a right basal pneumonia with evidence of consolidation; he had his crisis on the fourth day. The indigo varied between "1½" and "3" until the day after the crisis, when it returned to normal.

7 Pleurisy

This complication occurred in two cases (Nos. 48 and 86). In the former, the inflammatory condition was succeeded by an effusion and throughout the illness the amount of indigo continued raised. Three days after the chest was aspirated, the indigo returned to normal (see Chart VIII). In the latter case the excess of indigo varied with the pyrexia as noted in other inflammatory conditions.

8 Rheumatism

In seven cases this complication was met with and in six of these an excess of indigo varying between "2" and "4" was noted on the day of onset of symptoms (see Chart IX). In the case excepted, the increase oc-

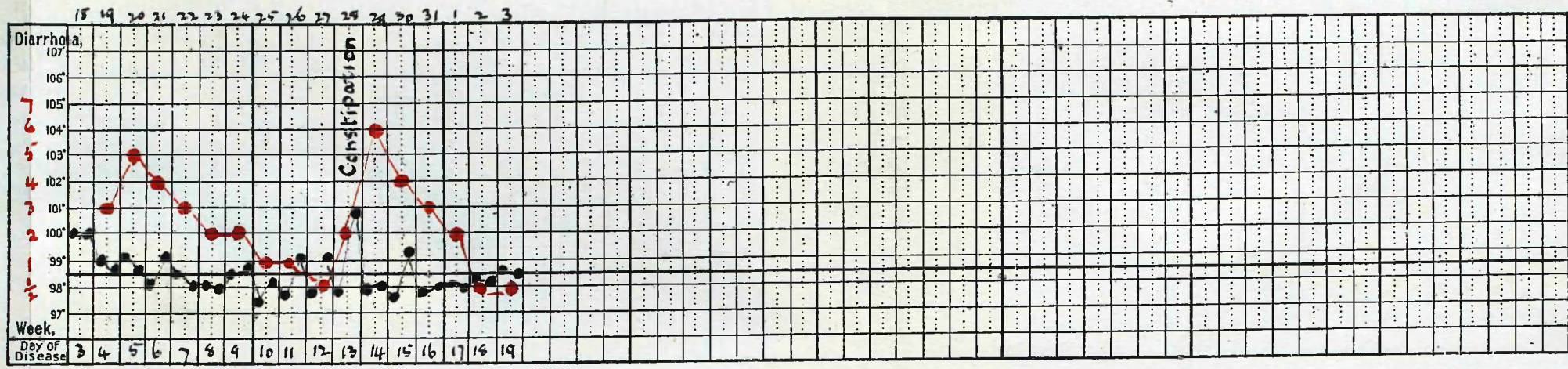
Chart X - showing effect of constipation on the index.

October November

Journal Reference,
S.D. (Case 74)
Sex, female Age, 4 yrs.

Result,
Complications,
Constipation

Remarks,



to face page 20

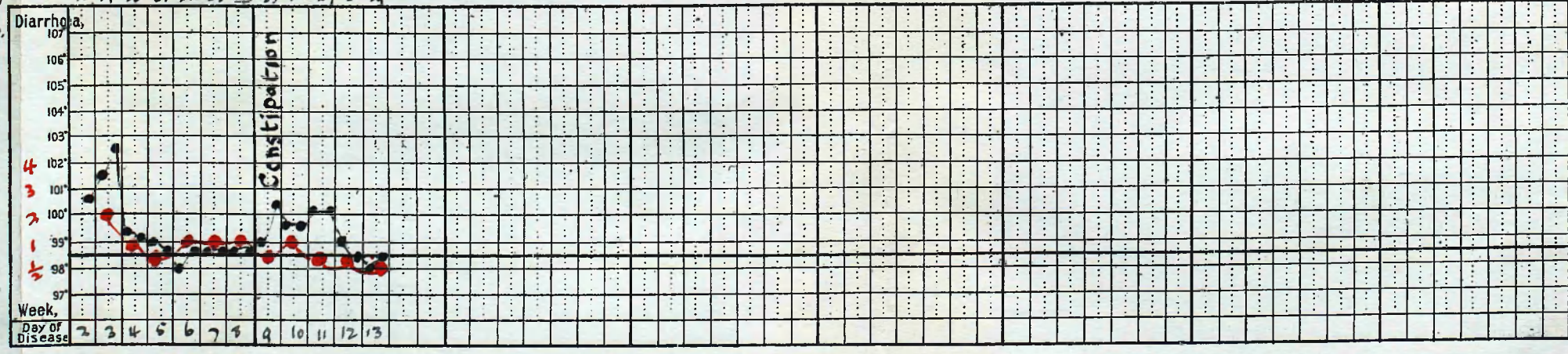
Chart XI - showing no increase in the index tho' constipated for 3 days (Case 62)

January

Journal Reference,
S.R. (Case 62)
Sex, female Age, 8 1/2 yrs.

Result,
Complications,
Constipation

Remarks,



to face page 20

curred two days before. The indigo returned to a normal level at a period varying between one and three days after the arthritic symptoms had disappeared.

9 Diarrhoea

Only two cases of diarrhoea occurred among the patients whose urines were being examined. In Case 19 it persisted for 2 days, on both of which the indigo was raised standing at "2" on the first day and at "3" on the second. It then returned to normal.

Case 59 was more severe in character and extended over a period of six days, during which time the indigo varied between "2" and "6"; it then gradually diminished in amount, becoming normal again four days later. These two cases correspond with Hochsinger's¹⁴ statement that "indicanuria is almost invariably present in grave forms of diarrhoea, but when the latter is of a mild type it appears less often and in smaller quantities."

10 Constipation

Eleven definite cases of constipation were observed, and nine of these, by shewing an increase in indigo in varying amount, bear out the general view that intestinal putrefaction is one of the chief sources of excessive indicanuria (see Chart X). In seven of these cases the constipation was unaccompanied by any rise of temperature, the indigo varied between "2" and "6" and returned to normal by the third day after the administration of aperients. Case 74 shewed a rise of temperature to 100.8° F., the indigo increased to as

Chart XV

showing Recurrence in Erysipelas with increase in the amount of indigo.

Journal Reference,

J. M. A. (Case 121)

Sex, male Age, 39 yrs.

October

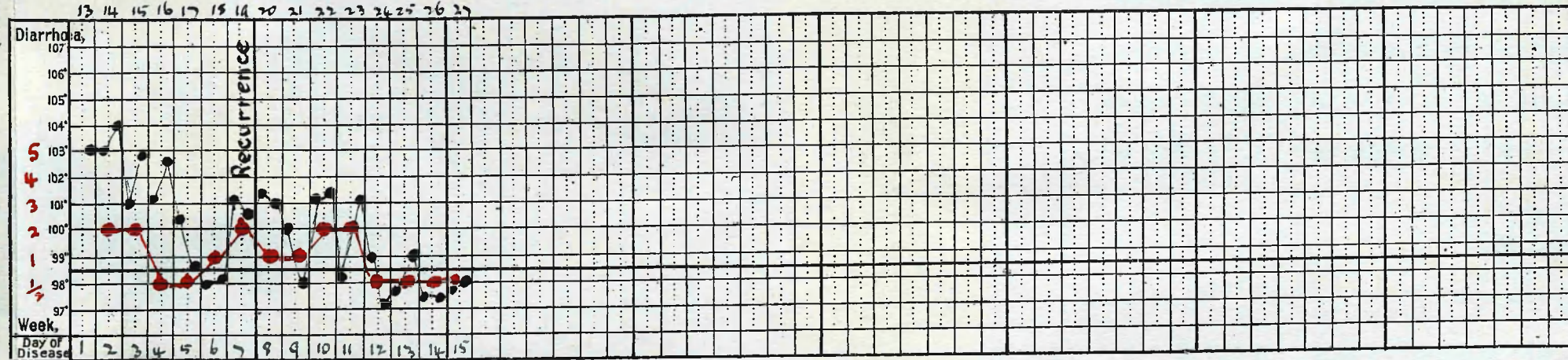
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

Result,

Complications,

Recurrence in Erysipelas.

Remarks,



high as "6" and did not return to the normal level until the fifth day. Case 76 was similar in every respect, except that the temperature rose to 102° F. These two last-mentioned cases were more severe, there was evidently more toxæmia as indicated by the temperature and by the excess of indigo extending over a longer period. Two cases (Nos. 62 and 63) shewed no increase in the amount of indigo, though both were constipated for three days and shewed a rise of temperature to 100.4° F. and 102.4° F. respectively (see Chart XI).

11 Phthisis

A great deal of controversy has arisen regarding the presence of indicanuria in tuberculosis. Herter,¹⁵ Hochsinger and Djouritch¹⁶ maintain that it is an important diagnostic feature, while Giarre,¹⁷ Cima¹⁸ and Gehlig¹⁹ hold an exactly opposed view. Although numerous cases of tubercle were present in the hospital, they were as a rule complicated in various ways: Case 15, however, after a mild attack of Measles was detained in hospital for a period extending over twelve weeks. The patient had a well marked lesion at the left apex, and during residence an excess of indigo averaging "3" was constantly present.

12 Relapse occurring in Erysipelas

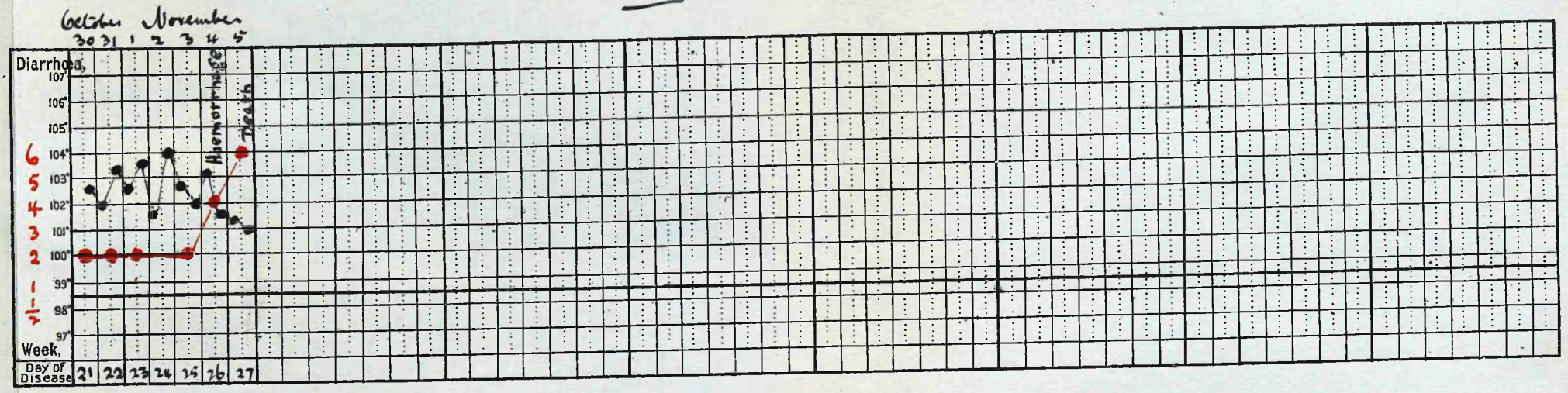
Six cases of relapse occurred among the cases of erysipelas under observation. Five of these shewed an increase in the amount of indigo varying between "2" and "4" and corresponding both to the onset and degree of pyrexia (see Chart XV). It returned to normal with

Chart XII. Increase of indigo with Haemorrhage in Enteric Fever. (Case 25)

Journal Reference,
R.B. (Case 25)
Sex, male Age, 23 yrs.

Result,
Death.
Complications,
Haemorrhage.

Remarks,



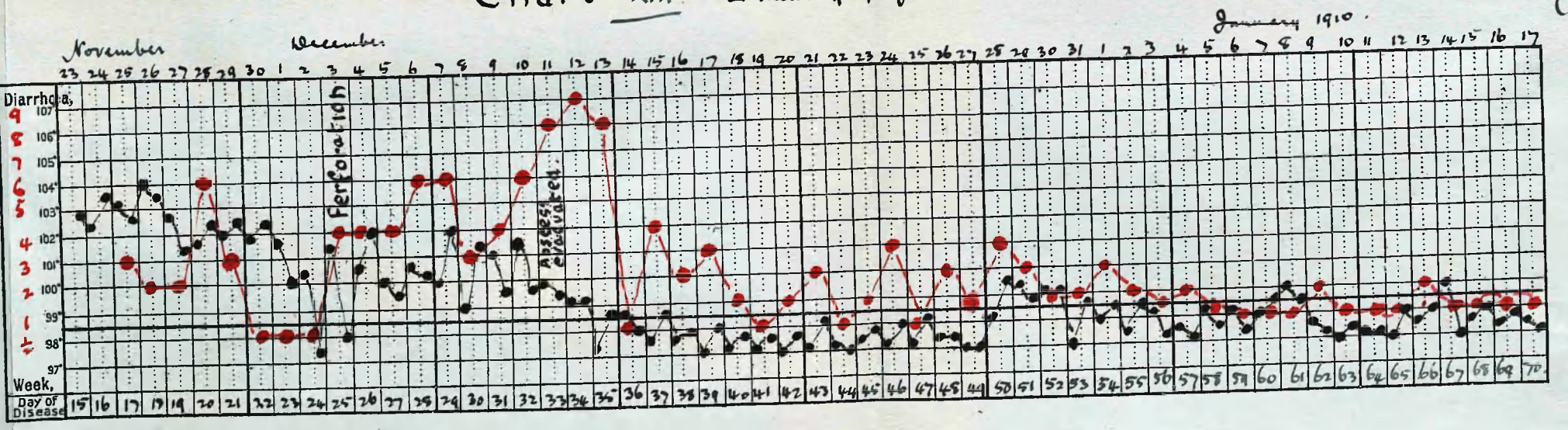
...maintain that it is an ...
...diagnostic feature, while ...
...hold an exactly opposite view. ...
...cases of tubercle were present in the hospital. ...
...they were in a rare complicated in various ways. Case ...
...however, after a mild attack of malaria was obtain

Chart XIII. Showing perforation in Enteric Fever followed by formation of a Pelvic Abscess. (Case 29)

Journal Reference,
J.M.S. (Case 29)
Sex, male Age, 25 yrs.

Result, Recovery.
Complications,
Perforation
Pelvic abscess.

Remarks,



to face page 27

the temperature. The exception (Case 129) was of a mild character, lasting two days: no rise of temperature occurred, but the indigo was raised to "4" and "2" on successive days before returning to normal.

13 Relapse occurring in Enteric Fever

Among the fifty-three cases of enteric fever whose urines were examined, eleven of these shewed a recrudescence or relapse. In all of them there was a rise in the amount of indigo at the onset of the pyrexial period and a return to normal at its conclusion (see paragraph on enteric fever).

14 Haemorrhage and Perforation occurring in Enteric Fever

Although the type of this disease prevalent at the time these observations were being conducted was unusually severe, yet complications were of very infrequent occurrence. There were but three cases of Haemorrhage and one of perforation.

Of the former cases two died. In all three the indigo increased markedly in amount at the time of the Haemorrhage, in cases 25 and 30 from "2" to "4" and in case 28 from "2" to "8" (see Chart XII). In the patients who died, the indigo remained high from this point onward until death, while in the patient who recovered (case 28) the indigo continued irregular between " $\frac{1}{2}$ " and "6" until the subsidence of the pyrexia sixteen days later.

In Case 29 who perforated, this complication occurred on the 25th day of illness. The indigo, prev-

Chart XIV - showing increase of indigo in toxemia.

Journal Reference,

B. M. (case 32)

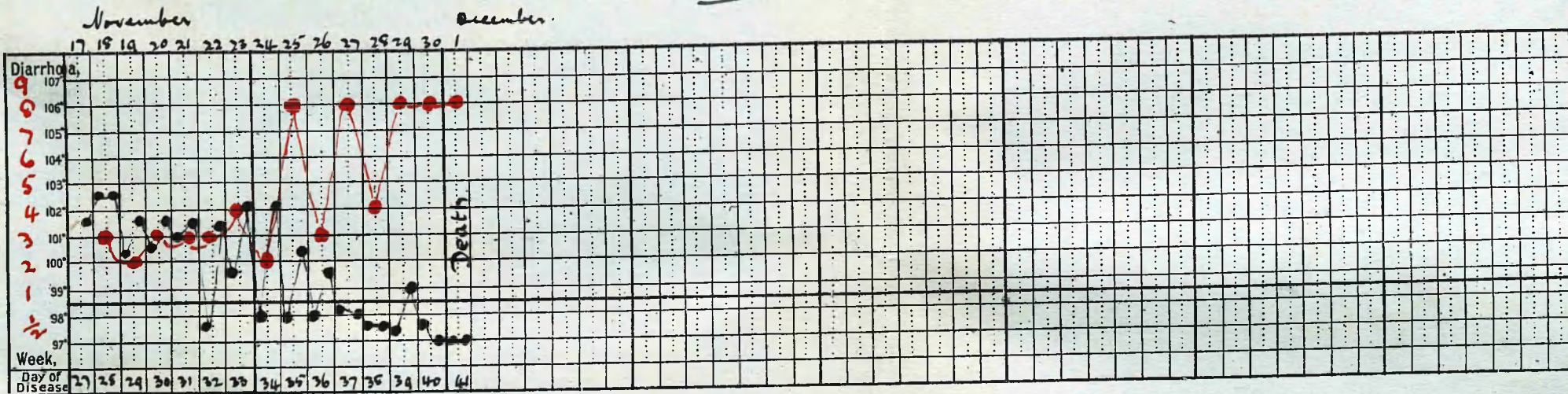
Sex, male Age, 40 yrs.

Result,

Death.

Complications,

Remarks,



iously normal for two days then rose to "2", and until his thirty third day of illness remained between "3" and "8". On that day a pelvic abscess was evacuated and from that time onward the amount of indigo gradually diminished (see Chart XIII).

(a) RELATION

of

INDICANURIA TO CASES WHICH TERMINATED FATALLY

Among the cases under consideration, fifteen resulted in death, seven of these occurring in Enteric Fever, four in Diphtheria, two in Scarlet Fever and one each in Measles and Erysipelas. Where the fatal issue was due to cardiac failure (as occurred in the four cases of Diphtheria and in one case of Scarlet Fever) nothing characteristic was noted, but where a gradually increasing toxæmia prevailed, the amount of indigo shewed a corresponding increase (see Chart XIV). Excluding two cases which terminated fatally after Haemorrhage, this occurred in eight cases: the increase varied between "3" and "8" and was therefore always marked. In three of the cases this increase developed seventy-two hours before death, in two cases forty-eight hours, in one case twenty-four hours, and in two cases twelve hours before death.

Judging from the few examples given above, the examination of the urine for indigo may prove to be of use as regards prognosis in toxic cases, quite apart from its significance in diseases of the intestinal tract as pointed out by Simon and regarded by him as a

test of equal importance with that of albumin: in those cases terminating suddenly, its presence may be of no prognostic value.

IV CLASSIFICATION OF CASES

It has been thought better to discuss the results of the investigation at an early portion of the paper (Section III), and the observations made upon each disease separately will now be given. The order in which the diseases are dealt with is as follows:-

- A Measles
- B Scarlet Fever developing Measles
- C Enteric Fever
- D Scarlet Fever
- E Diphtheria developing Scarlet Fever
- F Typhus Fever
- G Diphtheria
- H Erysipelas

A. MEASLES

The cases are divided into three groups, viz:- Severe, Medium and Mild.

The first group, the Severe, includes those cases in which the temperature was above 102° F. on admission. These number fifteen (15) among whom there was one death.

The Second Group, the Medium, includes those cases in which the temperature ranged between 100° F. and 102° F. on admission. These cases number forty-three, all of whom recovered. In the third group, the Mild, which includes fifty-six cases, the maximum temperature on admission was 100° F.

In Group I, the Severe, the amount of indigo present on admission was always high, except in one instance. On the day after admission the amount averaged "3.5" and ranged between "1" and "8": this gradually decreased to normal as the temperature subsided. In the exception above noted, the temperature became higher on the day after admission and the indigo increased from "1" to "6" and thereafter followed the course just described. In five of these cases there were complications.

CASE 1 - K. O'C. female, 5 years.

This patient developed nephritis on her seventh day of illness - her urine became clear twenty-four days later. During this time the amount of indigo present was irregular varying from " $\frac{1}{2}$ " to "8": two days after the disappearance of the albumin the indigo fell to normal (" $\frac{1}{2}$ ") and remained so (with only an occasional rise to "1") during convalescence (see Chart V).

CASE 2 - V. H., female, 13 years.

This patient developed an albuminuria on her tenth day of illness which persisted for six days: on its appearance, the indigo rose to " $2\frac{1}{2}$ " and returned to " $\frac{1}{2}$ " two days after the urine became normal.

CASE 3 - M. P., female, 7 years.

In this case, an abscess formed in either cheek a little below the eyelid: they were incised on the twenty-third day of illness. The indigo gradually increased to "1", "2" and "4" on successive days during the growth of the abscesses, and fell to normal the day after they were incised.

CASE 4 - J. M., male, 5 years.

Otorrhoea developed in this case on the twenty-

second day of illness: this complication succeeded a broncho-pneumonia and though the child's temperature had been normal for eight days, the indigo still remained high ("4"): it fell immediately the ear began to discharge, reaching normal four days later and remaining there.

CASE 5 - J. G., male, 5 years.

This patient suffered from broncho-pneumonia on admission and developed eanerum oris two days later, his sixteenth day of illness. He died ten days later. Throughout the course of the disease, the indigo was constantly high, varying between "2" and "8".

GROUP II: This group contains forty-one cases. These present during the acute part of the disease a smaller quantity of indigo than found in Group I, the average being "2.5" as compared with "3.5" in that group. Thirteen patients suffered from complications.

CASES 6 AND 7 - C. McK. female, 19 years and A. McL., female, 29 years.

These patients developed secondary sore throats on the sixteenth and nineteenth days of illness respectively: in both cases the amount of indigo rose and fell with the temperature, reaching "3" when the temperature was at its maximum (101° F.).

CASE 8 - J. G., female, 6 years, developed a cervical adenitis on the sixteenth day, with a temperature of 101.4° F.: her indigo rose from "½" to "3" and gradually fell with the temperature, reaching normal seven days later.

CASE 9 - A. W., female, 3½ years.

In this case multiple small abscesses were pres-

ent: the indigo fluctuated between "½" and "8" following the course of the temperature until convalescence was established.

CASE 10 - B. C., female, 6 years, Case 11, A. C., female, 10 years, Case 12 - M. S., female, 5 years, developed Bronchitis on their 8th, 21st and 26th days of illness respectively. In all three the amount of indigo was very high, reaching "8" and "10" in the two former cases and "8" in the latter (see Chart VII): as the temperature became normal the indigo diminished.

CASE 13 - S. S., female, 5 years.

This patient developed an albuminuria on her 9th day of illness - at the same time the indigo rose from "½" to "3", persisting in excessive quantity while the albuminuria lasted, and returning to normal with the restoration of the function of the kidneys. The albuminuria persisted for five days.

CASE 14 - D. C., male, 4 years.

In this patient cancrum oris appeared on the 5th day of illness. Operation was performed early and the patient recovered. During the period of pyrexia, lasting eleven days, the amount of indigo varied between "2" and "4" and with the disappearance of the former it resumed its normal level.

CASE 15 - Mrs C. female, 30 years, suffered from Phthisis on admission: the amount of indigo was constantly high, averaging about "3" during her twelve weeks residence in Hospital.

CASE 16 - H. McG., male, 6 years, is of some special interest and will be referred to later in connection with

Enteric Fever. No complication beyond constipation was present during convalescence, but the occurrence of this was followed by a marked rise of indigo in the urine ("3") which disappeared after the administration of aperients.

CASE 17,- R. B., male, 6 years and Case 18 - B. C., female, 6 years, developed Scarlet Fever on their 33rd and 42nd days of illness respectively and will be discussed in connection with the latter disease.

GROUP III - This group contains fifty-six cases. A still further diminution in the amount of indigo is noted, the average being "2" in the forty-seven cases from whom specimens of urine were obtained in the twenty-four hours following admission. In this group the temperature was in no case more than sub febrile, and in the bulk of cases normal, the day after admission. It is to be noted here that the return of the indigo to the usual amount did not follow the temperature so closely as in the preceding groups. It fluctuated generally for some days (and in some cases for as long as a week), suggesting that the phenomenon bore some relation to the elimination of toxins sufficient in amount in the previous cases to disturb the temperature and sufficient in these mild cases of measles to interfere with the alimentary processes for some period after the temperature had fallen.

Complications in this group occurred in only three cases.

CASE 19 - J. McC., male, 4 years, developed diarrhoea on his 5th day of illness - the indigo rose from " $\frac{1}{2}$ " to "2" and "3" on successive days, and then became normal again.

CASE 20 - A. McL., male, 4 years, developed an abscess on his buttock on his 35th day of illness. During its formation the amount of indigo rose to "2½" and returned to normal four days after the incision was made.

CASE 21 - J. F., female, 5 years, developed chicken-pox: four days previous to the appearance of the eruption the indigo gradually rose, reaching as high as "4": for the next 12 days it was irregular, but at the end of that time became normal again.

CASES 22 AND 23 were anomalous. Though no complication could be detected the amount of indigo in these cases ranged from "½" to "8" during the period of residence in Hospital.

The preceding remarks apply solely to the disease itself and to its complications. There is one other factor, however, which requires to be mentioned. In a large number of cases a secondary rise in the amount of indigo occurred after the patients were given a more liberal diet. This was especially marked in the severe and medium cases, among 70% of whom a considerable rise in indigo was observed for the first few days after the diet was increased. The alimentary tract in these cases seemed quickly to recover its tone, the excess of indigo disappearing in two or three days. This secondary rise did not appear at the same period in every case but varied in its onset from two to five days after the diet had been extended. This phenomenon was hardly noted among the mild type of cases.

B ADDENDUM TO MEASLES

Cases of Scarlet Fever developing Measles

In the ordinary course of events, patients when admitted into the wards have well-marked signs of the disease from which they are suffering, and therefore there is no opportunity of watching the behaviour of the indigo in the urine during the period of incubation or invasion. As it was found that the urines of convalescents in practically every case presented only a trace of indigo, this was regarded as normal, and when a ward became complicated, the urines of the convalescent patients were examined to see if there was any increase in the amount of indigo in the event of their developing another disease.

Among the cases of scarlet fever examined, nine developed measles. The result of the examination of these cases is to shew that in general there was no alteration in the amount of indigo during the incubation period, but it almost invariably rose during the period of invasion. In three cases, however, the last days of the incubation period were marked by a rise in the amount of indigo (Cases 77, 78 and 79).

The cases have been subdivided into three groups, according to the time at which the indigo began to increase in amount:-

- I Those where the indigo increased during the incubation period (Cases 77, 78 and 79)
- II Those where the indigo increased at the time the incubation period runs into the period of invasion (Cases 80 and 81)
- III Those where the indigo increased during the period of invasion (Cases 82, 83, 84 and 85).

As the number of cases is small, each individually is appended.

CASE 77 - D. L., male, 6 years.

This patient developed measles on the 15th day of illness. In his case the amount of indigo began to increase five days before the appearance of the eruption: it rose from " $\frac{1}{2}$ " to "2", the maximum "4" being reached two days later. When the rash appeared it stood at "2" where it remained. There was a rise of temperature to 100.4° F. on the 12th day of illness, but it subsequently returned to normal, to rise again to 103.4° F. on the appearance of the eruption. The temperature and the indigo returned to the normal level together three days later.

CASE 78 - J. M., male, 5 years.

This patient developed measles on the 31st day of illness: five days previously the indigo increased to " $\frac{1}{2}$ " where it remained until the temperature, which had risen to 101.4° F. on the day the eruption appeared, returned to normal five days later.

CASE 79 - E. D., female, 4 years

A measles eruption appeared on this patient on the 17th day of illness. Five days previous the indigo had increased to "2", on which day there was a preliminary rise in the temperature to 100.8° F. followed by a fall to normal: the following day the indigo rose to "6" and then fell to "4", "3" and "2" on successive days, the last being that on which the rash appeared - it then stood at "2", "4" and "2" on succeeding days returning to normal with the temperature the following day.

CASE 80 - L. C., female, $3\frac{1}{2}$ years.

This patient developed measles on the 11th day of illness. Four days before the appearance of the rash the indigo increased from " $\frac{1}{2}$ " to "1" and the following day to "2", the temperature at this time being normal: next day, however, the latter had risen to 101.6° F. and the following day when the rash appeared it was 104° F.: the indigo, however, remained stationary at "2" and subsided with the temperature a week later, a slight bronchitis having complicated the condition.

CASE 81 - N. McL., female, 3 years.

This patient developed measles on her 33rd day of illness. Four days before this, the indigo increased from " $\frac{1}{2}$ " to "1", then to "2" and "4" on successive days and was at the same level the following day when the rash appeared. The temperature rose to 101.4° F. on the 29th day of illness, and then became normal, to rise again to 100.2° F. on the appearance of the eruption. The indigo and the temperature gradually subsided, reaching normal six days later, a slight bronchitis having delayed the convalescence.

CASE 82 - E. McL., female, 5 years -

A measles eruption appeared on this patient on the 29th day after her attack of scarlet fever. Three days previous the indigo increased from " $\frac{1}{2}$ " to "2" and then fluctuated between " $\frac{1}{2}$ " and "8" (averaging "2") until the temperature subsided seventeen days later, her condition being complicated by a broncho-pneumonia of medium severity.

CASE 83 - D. S., male, $3\frac{1}{2}$ years.

This patient developed measles on the 17th day

after his attack of scarlet fever. Two days before the appearance of the rash the indigo increased to "2", and next day to "3", the temperature still being normal: the following morning when the rash appeared, the latter had risen to 101.4° F. but the indigo remained at "3" and diminished as the temperature fell two days later.

CASE 84 - J. McP., female, 7 years.

This patient developed measles on her 17th day of illness. No increase in the amount of indigo was noted until the day the rash appeared, when it rose from "½" to "2", her temperature then being 102° F. The following day the latter had risen to 105° F. and the amount of indigo to "6", but from that time both gradually diminished until the normal was reached six days later.

CASE 85 - A. McD., male, 5 years.

This patient developed measles on the 27th day of illness. The temperature rose to 100° F. the day before the appearance of the rash, but there was no increase in the amount of indigo. The following day, however, the temperature rose to 103° F. and the indigo from normal to "4". Both then slowly diminished, the former reaching the normal level two days before the indigo.

C ENTERIC FEVER

In this disease practically the same subdivision has been employed as in Measles.

The first group, the severe, includes those cases in which the temperature was 104° F. on admission, and

whose temperature of remission varied about 103° F. These cases number eleven, of whom four died.

The second group, the Medium, includes those cases in which the temperature ranged about 103° F. as maximum with a remission in some cases to 99.2° F.

In the third group, the Mild, the maximum temperature range varied from 101° F. to 102° F.

In Group I, the Severe, specimens of urine from six of the eleven cases were obtained within twelve hours of admission: the amount of indigo varied between "1" and "6" and averaged "3". Throughout the course of the fever the amount of indigo present was high, and those cases that presented only a small amount in the first twenty-four hours shewed an increase to as much as "8" within the next three or four days: in all the cases that recovered, the indigo gradually decreased to normal with the temperature.

(a) Cases with Complications which ended in Death

CASE 24 -

Of the patients who died, one, W. S., male, 11 years, shewed a large amount of indigo throughout. His temperature became normal on the 19th day after admission, but two days later a relapse occurred with a corresponding increase in the amount of indigo. At the end of a fortnight his temperature had reached normal, but during the following seven days it was subnormal (97° F.) due to a low form of peritonitis from which he died. The indigo remained high during the relapse, but was normal during the "afebrile" period, suddenly rising to "8" twelve hours before death on the 60th day of illness.

CASE 25 - R. B., male, 23 years.

This patient was admitted on his 21st day of illness, suffering from a severe attack of enteric fever. The amount of indigo was a little raised, standing at "2". On the 26th day of illness he had a severe haemorrhage, from the effects of which he died the following day. Twenty-four hours before the complication occurred the amount of indigo had begun to increase, and the maximum ("6") was reached on the day of his death (see Chart XII).

CASE 26 - J. C., male, 37 years.

This patient had a very severe toxæmic attack of Enteric Fever and died four days after admission on the 13th day of illness. The amount of indigo was raised on admission ("1½") and rose continuously until the day of his death when it reached "3".

CASE 27 - E. D., male, 29 years.

This patient was admitted on his 17th day of illness, suffering from a severe toxic attack of enteric fever: he died two days later of cardiac failure. Though not in excess on admission, the amount of indigo rose gradually to "3" on the last day of illness.

(b) Cases with complications which ended in recovery

Only two cases come under this heading.

CASE 28 - A. W., male, 32 years.

This patient suffered from a severe toxæmic attack of enteric fever with haemorrhage on his 19th day, and small ones on his 22nd, 29th and 30th days of illness. The amount of indigo fell from "6" to "2" twelve hours before the haemorrhage, and rose to "8" the fol-

lowing morning, which was the highest point recorded during his illness. The diminution was associated with a fall of temperature from 101.8° F. to 99.8° F. No appreciable alteration in the amount was observed on the occurrence of the smaller haemorrhages.

CASES 29 - J. McG, male, 25 years.

This patient had a severe attack of enteric fever complicated by perforation of the bowel on the 25th day of illness. The amount of indigo rose from "½" to "4" on this day and during the succeeding fortnight remained between "8" and "10", associated with the development of a pelvic abscess: when this was evacuated it quickly decreased. A faecal fistula formed and persisted for 10 weeks and the amount of indigo for the first three weeks of this time varied between "1" and "3", and then, becoming normal, remained so (see Chart XIII).

GROUP II contains twenty-six cases. In twenty-two of these specimens of urine were obtained within twelve hours of admission. The amount of indigo was less than in the preceding group, averaging almost "2" and ranging between normal and "4". As in the "severe" type, the amount subsequently increased, though to a less extent than in Group I, and remained raised while the pyrexia lasted. Three patients in this group died.

(a) Cases with Complications which ended in Death

CASE 30 - P. C., male, 29 years.

This patient suffered from only a moderate attack of enteric fever. A severe haemorrhage, however, occurred on his 23rd day of illness, and a series of lesser haemorrhages began on the 26th day and continued for

four days. The patient's condition after this progressively became worse and he died of cardiac failure on the 34th day of illness. The amount of indigo rose from "2" to "4" on the day of the haemorrhage and remained at that level until the day before his death, on which the last specimen of urine examined was obtained.

CASE 31 - W. M., male, 57 years, was admitted during a relapse following an ambulant type of enteric fever, and died of cardiac failure on his 42nd day of illness, fourteen days after admission. The amount of indigo gradually increased from "2" on the day of admission, reaching to the maximum "6" on the day of his death.

CASE 32 - B. M., male, 40 years.

This patient was admitted during a relapse and died on his 41st day of illness, fifteen days after admission. The indigo was "3" on admission and rose in a remittent fashion for a week previous to death, reaching as high as "8", where it remained during the last three days of illness (see Chart XIV).

(b) Cases with Complications which ended in Recovery

Seven cases come under this heading. In four instances relapse occurred and the remainder had recrudescences.

CASE 33 - J. R., male, 25 years.

This patient suffered from a moderate attack of Enteric Fever, ending on the 26th day and followed by relapse. On the 28th day of illness, the temperature rose to 102° F. and remained elevated with daily remis-

sions for eleven days. The amount of indigo increased from " $\frac{1}{2}$ " to "2" on the first day and remained at " $\frac{1}{2}$ " during the pyrexial period, falling to " $\frac{1}{2}$ " again when the temperature became normal.

CASE 34 - J. McL., male, 28 years.

This patient's temperature reached normal on the 20th day of illness and three days later rose again. It then ran intermittently between 97.4° F. and 102.2° F. for the succeeding fortnight. The indigo, which had been normal, rose with the temperature to "3" and remained raised throughout the relapse, only returning to " $\frac{1}{2}$ " on the termination of the pyrexia.

CASE 35 - Mrs A., female, 50 years.

At the end of the 5th week of illness, after the pyrexia had subsided for seventeen (17) days, this patient's temperature again began to rise and varied intermittently between 98.4° F. and 102.4° F. for twelve days. The amount of indigo increased to " $2\frac{1}{2}$ " during this period, becoming " $\frac{1}{2}$ " again on the last day of the fever.

CASE 36 - Mrs M., female, 28 years, developed a relapse lasting a fortnight. The amount of indigo increased to "2" at the onset of the relapse remaining at this level during the course and falling to " $\frac{1}{2}$ " with its termination.

CASE 37 - J. McK., male, 3 years)
 CASE 38 - S. C., female, 11 years)

These patients developed a recrudescence on the 24th and 46th days of illness respectively. Both showed an increase during the pyrexial period from " $\frac{1}{2}$ " to "2".

In another instance, however, Case 39, A. G. female, 10 years, this correspondence between pyrexia and the amount of indigo was not observed. This patient shewed a rise of indigo to "2" in the first two days of the recrudescence, but it was normal for the remainder of the pyrexial period though the temperature ran a remittent course ranging between 99° F. and 103° F. for 10 days.

In Group III there are 16 cases. The amount of indigo present in the specimens obtained in the first twelve hours is slightly less than in the second group, averaging just over "1.5". It diminished as the temperature fell but did not follow the temperature so closely as in the severer cases and fluctuated more.

Three of the patients had recrudescences, viz:-

CASE 40 - H. W., male, 11 years, Case 41 - G. McT., male, 12 years, Case 42 - M. B., female, 9 years, beginning at the commencement of the 7th week, middle of the 4th week and middle of the 8th week respectively. They all shewed a rise in the amount of indigo to "2" at the onset of the complication and it remained elevated until the temperature became normal.

D SCARLET FEVER

In this disease the subdivision employed is as follows, namely, into three groups, Severe, Medium and Mild. The first group, the severe, includes those cases with a temperature of over 102° F. on admission. They number thirty cases, of whom one died.

The second group, the Medium, includes those cases

with a temperature of between 100° F. and 102° F. on admission. They number 45 cases, with one death.

In the third group, the Mild, in which there are thirty-three cases, the maximum temperature on admission was 100° F.

In Group I (the Severe) specimens of urine were only obtained in fifteen out of thirty cases within twelve hours of admission - this is explained by the fact that the patients were severely ill and the majority young female children.

The amount of indigo present in these first specimens averaged "2" and varied between "1" and "6": by next day a decided increase was observed averaging "3" over twenty-nine of the thirty cases examined. In all the cases which recovered, the amount of indigo remained high from this point until the termination of the pyrexia when it became normal.

In Case 43, E. T., female, 4 years, who died, the child suffered from a very severe septic attack of scarlet fever, which terminated fatally on the 17th day, 12 days after admission. The urine was examined on six of the days and the amount of indigo present averaged "8": it was increasing three days before death but no specimen was obtainable during the last forty-eight hours.

Ten of these cases suffered from complications.

CASE 44 - M. McP., female, 4 years.

This patient developed otorrhoea on the 16th day of illness: five days before the membrane perforated the amount of indigo rose from "1" to "3½" and remained high until the discharge commenced, when it diminished and became normal two days later.

CASE 45 - W. S., male, 11 years

On the 41st day of illness the temperature rose

to 99.4° F. and he developed a secondary attack of scarlet fever: the amount of indigo gradually increased from normal to "3" during the three days preceding the onset of symptoms, but after the appearance of the rash it began to diminish and became normal three days later.

CASE 46 - D. C., male, 28 years.

On his 35th day of illness this patient's temperature rose to 100° F. and remained at that level for three days: with the onset of the pyrexia he complained of pains in his wrist and ankle joints. The amount of indigo was only increased above normal on one day, namely, the day of onset of symptoms, when the amount observed was "4".

CASE 47 - J. M., male, 8½ years.

This patient suffered from nephritis on admission: his temperature was 102° F., but there was only an increase to "1½" in the amount of indigo, which returned to normal again four days after the disappearance of the albumin.

CASE 48 - H. C., female, 13 years.

This patient was very ill on admission: pleuritic friction was detected on the 5th day, and on the 15th day of illness twelve ounces of fluid were withdrawn from the chest: during this time the amount of indigo fluctuated between "1" and "3" (averaging "2") and became normal three days after the chest was aspirated (see Chart VIII).

CASE 49 - M. L., female, 4 years.

On the 7th day of her illness, this patient became constipated: on the same day the amount of indigo increased to "6", where it remained for three days and,

then returned to normal after the administration of aperients.

CASE 50 - G. McC., male, 7 years.

This patient suffered from a severe attack of scarlet fever - his cervical glands were enlarged on admission and eight days later they were incised: two days previous to the incision the amount of indigo increased from "1" to "6", but it immediately began to diminish after the operation and was normal again three days later (see Chart III).

CASE 51 - E. McC., female, 12 years.

On the 17th day of her illness this patient's submaxillary glands became enlarged: the temperature rose to 99.2° F. and fluctuated between this and 100.6° F. for seven days. At the onset of the complication the amount of indigo increased from "1" to "6" and then gradually decreased, to become normal three days later (and three days before the temperature) on the 22nd day of illness.

CASE 52 - M. L., female, 4 years.

This patient's submaxillary glands became enlarged on the 24th day of illness: the temperature rose to 99.6° F. and next day it reached 102.8° F., becoming normal two days later. The amount of indigo reached "6" and "8" respectively on the first two days of the complication and then diminished, becoming normal six days later (see Chart II).

CASE 53 - W. S., male, 11 years.

This patient developed a septic finger on his 20th day of illness: the amount of indigo increased from "1" to "3", where it remained for three days and then became

normal.

GROUP II, the Medium, contains forty-five cases, of which one terminated fatally. The amount of indigo varied between normal and "4" on admission and averaged "2". In the cases which showed a marked quantity on admission the amount of indigo subsided with the pyrexia. Even in those cases where it was normal or small in amount on admission, it was noticed that some variations in the amount occurred until the temperature had become settled.

(a) Case which ended in death

CASE 54 - J. B., male, 4 years.

Altho' this patient's temperature leads to his inclusion in this group, yet he suffered from a severe attack of scarlet fever complicated with a marked albuminuria. He died of cardiac failure on the 19th day of illness, fifteen days after admission. The temperature varied between normal and 102.6° F. and showed daily remissions of between two and three degrees. The amount of indigo fluctuated between "½" and "2" during his illness and during the last three days remained practically normal.

(b) Cases with Complications which ended in Recovery

CASE 55- F. McF., male, 3 years.

This patient developed a double otorrhoea on the 9th day of illness. On the day previous, the indigo increased from "½" to "2", but fell to normal again the day after the discharge commenced. On the 15th day of

illness he developed a paronychia in his right thumb and three days later the left thumb became affected in the same way - during this period the indigo varied between "1" and "4", returning to normal two days after the last incision was made.

CASE 56 - A. T., female, 6 years.

On the 7th day of this patient's illness her submaxillary glands became enlarged, accompanied by a rise of temperature to 100° F: it remained at this level for four days and then slowly fell, reaching normal three days later. The amount of indigo rose with the temperature from " $\frac{1}{2}$ " to "3", remained high for three days, and then gradually fell, becoming normal again the day after the pyrexia.

CASE 57 - D. L., male, 6 years.

On the 28th day of illness this patient's submaxillary glands became enlarged, associated with a rise of temperature to 100.8° F. for a single day. The amount of indigo increased from " $\frac{1}{2}$ " to "2" two days previous to the elevation of temperature, and remained between "2" and "3" for a week, when it returned to normal.

CASE 58 - H. W., male, 7 years.

This patient's submaxillary glands became enlarged on the 38th day of illness: on that day his temperature rose to 99° F. and the amount of indigo increased from " $\frac{1}{2}$ " to "2": it remained between "2" and "3" for a week, during which time the glandular enlargement persisted, and then returned to normal.

CASE 59 - L. C., female, $3\frac{1}{2}$ years.

This patient had a severe attack of enteritis,

which began on the 36th day of illness and persisted for six days. The number of stools per day varied between "4" and "10" - they were loose and contained blood and mucus. During this period the indigo varied between "2" and "6", and returned to normal four days after the cessation of the diarrhoea.

CASE 60 - A. McD., male, 5 years.

This patient developed a broncho-pneumonia on the 37th day of illness: his temperature varied between 98° F. and 105° F. for a period of twelve days, when it returned to normal. The indigo was raised from "½" to "2" during the first three days of illness, but was not elevated above "1" during the last nine days of pyrexia.

CASE 61 - M. McC., female, 7 years.

This patient developed a mild attack of Rheumatism in her wrist-joints on her 7th day of illness - her temperature rose to 101° F. and the amount of indigo from "½" to "2", both returning to normal two days later (see Chart IX).

CASE 62 - S. R., female, 8½ years.

- " 63 - T. M., male, 2½ "
- " 64 - A. S., female, 12 "
- " 65 - C. McC. " 3 "

These patients all suffered from constipation. In the first-named, it continued for three days, accompanied by an increase of temperature to 100.4° F. The indigo was not raised above "1" (see Chart XI). In the second case, the temperature rose to 102.4° F. and then slowly fell, reaching normal three days later. No increase in the amount of indigo was observed.

In the third and fourth cases there was no rise of

temperature, but the indigo increased to "4" and "2" respectively, returning to normal after the bowels had been well moved by aperients.

GROUP III, the Mild, contains thirty-three cases, all of whom recovered. The amount of indigo on admission varied between " $\frac{1}{2}$ " and "4" and averaged "2": in those cases where the temperature became higher next day, there was a corresponding increase in the amount of indigo. As in the two previous groups, the indigo became stationary at normal on the termination of the pyrexia.

Eleven of the cases in this group developed complications.

CASE 66 - A. T., female, $9\frac{1}{2}$ years.

On the 7th day of illness this patient's submaxillary glands became enlarged: her temperature rose from normal to 100° F. and the indigo increased from " $\frac{1}{2}$ " to "4". Both returned to normal next day.

CASE 67 - E. D., female, 4 years.

This patient developed a discharging ear on the 42nd day of illness. Four days previous the amount of indigo had increased from " $\frac{1}{2}$ " to "2", and it remained at this level until the day after the discharge made its appearance, when it became normal.

CASE 68 - J. D., male, 14 years.

On the 51st day of illness this patient's left ankle joint became painful. His temperature rose to 102° F. and the indigo increased from " $\frac{1}{2}$ " to "2": both returned to normal two days later.

CASE 69 - H. H., male, 7 years.

This patient developed a severe attack of nephritis on his 32nd day of illness. His temperature rose to

101.8° F., and the indigo increased to "8", though it returned to normal three days later. The albuminuria persisted for eight weeks longer, though there was no further rise in the amount of indigo.

CASE 70 - K. H., male, 16 years

" 71 - L. McL., female, 7 years

These patients developed an albuminuria on the 36th and 18th days of illness respectively. In the former case the amount of indigo increased from normal to "2" where it remained for two days, when both urine and indigo became normal. In the latter case the albuminuria persisted for a fortnight. On the day of its appearance the indigo rose from " $\frac{1}{2}$ " to "2", and then fluctuated between " $\frac{1}{2}$ " and "3" while the albumin was present, and returned to normal the day after it disappeared.

CASE 72 - J. McD., female, 5 years

" 73 - A. T., " 9 "

" 74 - E. D., " 4 "

" 75 - M. P., " 13 "

" 76 - M. McG., " 12 "

These patients all suffered from constipation.

In cases 72 and 73, the indigo rose to "2" and then became normal. There was no rise of temperature.

Case 74 shewed an increase to "2" on the first day and to "6" the following day, and then gradually diminished to "4", "3", "2" and normal on successive days. The temperature was raised to 100.8° on the first day only (see Chart X).

In Case 75, the temperature rose to 100° F. and the indigo increased from " $\frac{1}{2}$ " to "2", becoming normal again next day.

In Case 76, the temperature rose to 102° F. and then slowly came down, reaching normal four days later. On the first day the indigo increased to "2" and then to "6" on the following day, after which it stood at "4", "2" and " $\frac{1}{2}$ " on successive days.

E. ADDENDUM TO SCARLET FEVER

Cases of Diphtheria developing Scarlet Fever

When a case of Scarlet Fever occurred in a Diphtheria ward, the urines of the convalescents were examined with a view to ascertaining whether, in the event of their taking the disease, there was any alteration in the amount of indigo present during the period of incubation.

Seven cases, convalescent from Diphtheria, developed Scarlet Fever, and the results of the examination go to shew that in five of these there was a distinct rise in the amount of indigo during the period of incubation. In three cases this occurred four days before the rash appeared and in two cases three days before: in the remaining two cases the rise occurred the day before the appearance of the rash, and therefore corresponded with the onset of the period of invasion. In three of the seven cases there was a still further increase during the first twenty-four hours of the invasive period, but in all, the amount of indigo returned to normal when the temperature subsided. The seven cases are appended individually.

CASE 111 - J. T., male, 4 years.

This patient developed a mild attack of Scarlet Fever on the 30th day of his attack of Diphtheria. Three days prior to the appearance of the rash, the indigo increased from " $\frac{1}{2}$ " to "2", where it remained until the temperature became normal on the 31st day of illness, when it became " $\frac{1}{2}$ " again.

CASE 112 - D. H., female, 6 years.

This patient developed a sharp attack of Scarlet Fever on the 67th day of illness. Three days before the rash appeared, the indigo increased from normal to "3" - it then remained at "2" for two days, then at "1", becoming normal with the temperature four days later.

CASE 113 - H. F., female, $6\frac{1}{2}$ years.

This patient developed a mild attack of Scarlet Fever on the 56th day of illness. The day before the appearance of the rash, the indigo increased from " $\frac{1}{2}$ " to "3" - it then became "2", "1" and " $\frac{1}{2}$ " on successive days, the latter occurring on the day the temperature became normal.

CASE 114 - A. D., female, 3 years.

This patient developed a mild attack of Scarlet Fever on the 21st day of illness. Four days before the rash appeared the indigo increased to "1" where it remained for three days. It then increased to "3" on the day the rash appeared and the temperature rose to 101° F. The following day it had returned to normal with the temperature.

CASE 115 - R. D., male, 8 years.

This patient developed a severe attack of Scarlet Fever on the 27th day of illness. Four days before the

appearance of the rash the indigo increased to "4": it then returned to " $\frac{1}{2}$ " for two days, and rose to "2" when the temperature went up to 101° F., on the day the rash appeared. For the next ten days, while the pyrexia persisted, the indigo fluctuated between " $\frac{1}{2}$ " and "6", temperature and indigo returning to normal at the same time.

CASE 116 - A. M., male, 7 years.

This patient was seized with a sharp attack of Scarlet Fever on the 29th day of illness. Two days earlier the indigo increased from " $\frac{1}{2}$ " to "2": it then returned to " $\frac{1}{2}$ " for two days, to increase again to "6" when the temperature rose and the rash appeared. The pyrexia persisted between 99° F. and 104° F. for eleven days, during which time the indigo fluctuated between " $\frac{1}{2}$ " and "6", returning to normal at the same time as the temperature.

CASE 117 - H. S., male, 5 years.

On the 41st day of his illness, this patient developed a mild attack of Scarlet Fever. On the day before the indigo increased from " $\frac{1}{2}$ " to "2", where it remained for four days, then becoming normal with the temperature.

F. TYPHUS FEVER

During the past winter a few sporadic cases of this disease were admitted into the wards of this Hospital, and the opportunity was taken of examining the urines of the patients admitted since this investigation began. They number eleven, all of whom recovered. The specimens were examined daily throughout the course

of the disease.

No subdivision according to the severity of the disease is required, as the temperature on admission over all the cases averaged 103° and varied between 102.6° and 103.8° F. The amount of indigo during the period of pyrexia was more or less raised in every case: it varied between "1" and "4" and averaged "2". It did not remain constantly high during this period but fluctuated between normal and "4", only remaining at the normal level after the occurrence of the crisis.

Complications occurred in only three cases.

CASE 86 - E. H., male, 43 years.

This patient suffered from a severe attack of Typhus Fever. On the 28th day of illness he complained of sore throat and his temperature rose to 101.4° F. where it remained for two days and then became normal. The indigo rose to "2" from normal on the first day of pyrexia and to "3" on the following day, then gradually diminishing in amount until it reached " $\frac{1}{2}$ " three days later. On the 41st day of illness he complained of pain in his chest and his temperature rose from 98.4° F: to 100.8° F: it remained elevated for eight days, during which time he suffered from a well-marked pleurisy. The indigo, previously normal, rose to "1" on the first day of the complication and then to "2", subsequently standing at "3" for two days before gradually returning to normal, which was reached the same day as the temperature subsided.

On the 107th day of illness, he developed rheumatism in his ankle, knee and wrist joints: the temperature rose to 101° F. and remained between 99.6° F. and 102° F. for eight days, when it returned to normal. The indigo increased from " $\frac{1}{2}$ " to "1" during the first

three days of the complication, and to "2" during the succeeding three: it then returned to "1" and next day became normal.

CASE 87 - B. N., female, 16 years.

This patient had her crisis on the 7th day of illness, but on the 9th day her temperature again became elevated owing to the development of furunculosis on the neck and scalp. An irregular pyrexia continued for a week and the indigo, which had returned to normal, again began to fluctuate between " $\frac{1}{2}$ " and "2". Three incisions were made in the scalp and from that time the indigo kept at a normal level.

CASE 88 - E. J., female, 8 years.

On the 13th day of illness this patient had her crisis, after an attack of Typhus Fever of moderate severity. The following day her temperature rose to 102° F. and she presented well marked signs of a right basal pneumonia, the crisis occurring three (3) days later. At the time of her Typhus crisis, the amount of indigo fell from "2" to " $\frac{1}{2}$ ", but the following day when the pneumonia developed it rose to " $1\frac{1}{2}$ " and the next day to "3": it remained at "2" for the next three days and then returned to normal, where it remained.

G. DIPHTHERIA

In this disease subdivision according to the temperature as employed in the description of the other fevers could not be used, as very severe cases frequently shew a normal or only a slightly raised temperature.

The cases have been subdivided into three groups according to the degree of toxæmia on admission. This

was determined partly by the opinion of the physician under whose care they were placed and partly by the amount of serum administered.

The first group, the Severe, contains nineteen cases, five of whom died. No case in this group received less than 10,000 units of serum. Specimens of urine were obtained in seventeen of the cases within twelve hours of admission, and the amount of indigo in these varied between "1" and "6", averaging "2.6". In the cases which recovered, the day on which the indigo reached normal varied between the third and the twelfth, but in the great majority of cases was the seventh or eighth day.

Eight of the cases developed complications.

(a) Cases with Complications which ended in Recovery

CASE 89 - J. W., male, 13 years.

This patient developed an albuminuria, persisting only for three days, on the 28th day of his illness - two days previously the indigo rose to "1" and the next day to "2", then returning to normal where it remained.

CASE 90 - P. S., female, $2\frac{1}{2}$ years.

On the 42nd day of her illness this patient's right ear commenced to discharge, her temperature rising to 100° F. at the same time: the day previous the indigo rose from " $\frac{1}{2}$ " to "2", returning to normal the day after the discharge commenced.

CASE 91 - J. B., male, 10 years.

This patient's cervical glands became enlarged on the 27th day of illness: two days previous the indigo rose from " $\frac{1}{2}$ " to "3", the temperature being normal: the

following day, when the temperature rose to 100.2° F., it stood at the same level, and on the two subsequent days at "2", after which it became normal.

CASE 92 - R. McK., male, 6 years.

This patient's cervical glands became enlarged on the 6th day of his illness: his temperature rose to 102.4° F. on that day and then slowly subsided, to become normal two days later. The indigo increased from " $\frac{1}{2}$ " to "2" the day before the glandular enlargement was noted - it then stood at "1" for two days, returning to " $\frac{1}{2}$ " next day, the same day as the temperature became normal.

(b) Cases with Complications which ended in Death

CASE 93 - T. McL., female, $1\frac{5}{12}$ years.

This child suffered from a severe haemorrhagic attack of Diphtheria, from which she died on the 15th day of her illness. During her residence the indigo fluctuated constantly between " $\frac{1}{2}$ " and "6", often being high when the temperature was normal. The indigo returned to " $\frac{1}{2}$ " two days before death, and shewed no subsequent rise.

CASE 94 - E. A., female, 9 years.

This patient died on the 20th day of her illness of pyelitis. The indigo fluctuated between "1" and "6" for the first twelve days of illness, during which time the temperature was normal. During the last five days of life, when the temperature remitted between 98.4° F. and 102.8° F., the indigo remained at "1".

CASE 95 - P. W., female, 4 years.

This patient suffered from a severe toxic attack

of Diphtheria, with laryngeal obstruction for which tracheotomy had to be performed: she died on the 7th day of illness. The indigo fluctuated between " $\frac{1}{2}$ " and "5" during her six days residence in Hospital.

CASE 96 - T. McN., male, 6 years.

This patient had a severe toxic attack of Diphtheria and died suddenly from cardiac failure on the 46th day of illness. There was no increase in the amount of indigo prior to death.

CASE 97 - P. S., female, $2\frac{1}{2}$ years.

This patient died of tubercular meningitis four months after admission, two weeks after this series of examinations had concluded. For a period of five weeks prior to the development of cerebral symptoms, she suffered from a broncho-pneumonia, during which time the indigo, which had hitherto stood at normal, fluctuated between " $\frac{1}{2}$ " and "3".

The second group, the Medium, contains thirty-five cases, of whom one died. The amount of indigo present on admission is slightly less than in the previous group, averaging exactly "2" and varying between the same limits. As before, the tendency for the indigo to return to a normal level at the end of the first week is noted in the great majority of cases. In nine of the cases complications occurred (excluding those that developed a secondary disease).

CASE 98 - S. C., female, 9 years.

This patient suffered from an attack of Diphtheria of moderate severity. The temperature became normal two days after admission, but the indigo remained between "3" and "4" for a further four days and then rose to "6": the following day the left ear commenced to

discharge and the indigo fell suddenly to "1". Ten days later the indigo increased from " $\frac{1}{2}$ " to "3" and the next day, when it had returned to normal, the right ear was found to be discharging (see Chart IV).

CASE 99 - A. S., female, 10 years.

On the 13th day of illness, this patient developed a serum rash and three days later her temperature rose to 101.4° F. It remained between 100° F. and 102° F. for three days, during which time she had pains in her wrist, ankle and elbow joints. On the 20th day of illness her temperature was normal, and the rash and pains had disappeared. Since the development of the rash the indigo had been slightly raised (standing at "1"), and on the day the joint pains appeared it increased to "2", returning to normal three days after the arthritic symptoms had disappeared.

CASE 100 - A. W., female, 39 years.

This patient suffered from a moderate attack of diphtheria complicated by a long-standing paralysis. In her 4th week of illness she developed pains in her ankles and knees, which became swollen and tender: the elbows became affected a week later. The indigo increased to "2" two days before the arthritic symptoms developed, and during the three weeks they persisted the indigo fluctuated between " $\frac{1}{2}$ " and "3", returning to normal after they had subsided.

CASE 101 - A. McL., female, 7 years.

This patient developed symptoms of bronchitis on her 35th day of illness, lasting five days: the indigo fluctuated between "1" and "6" for three days and then became normal again.

CASE 102 - A. W., female, 9 years

" 103 - W. C., male, 7 "

The urines of both these patients were normal on admission, but albuminuria developed later, the former on the 9th day and the latter on the 17th day of illness. No increase in the amount of indigo occurred in the former case, but in the latter it went up to "2" on the day before the albuminuria appeared and to "4" the following day: during the next eleven days, while the albuminuria persisted, the indigo fluctuated between " $\frac{1}{2}$ " and "6", and then returned to its normal level.

CASE 104 - C. T., female, 3 years

" 105 - M. M., male, 4 "

Both these patients developed enlarged cervical glands in the 3rd week of their illness. In the former case the indigo increased to "2" three days before the swelling appeared and remained at that level until the swelling subsided a week later - the temperature during this time running between 99° F. and 102° F. In the latter case the glandular enlargement was not so marked, the temperature being raised to 100° F. for three days. During this time the indigo ranged between "1" and "3".

CASE 106 - J. W., male, 9 years.

This patient also developed enlarged cervical glands, at the end of the 2nd week of illness. For three days his temperature fluctuated between 98.4° F. and 102.6° F. and the indigo between "1" and "4": at this point the swelling was incised, and the indigo fell to "2" next day and was normal the day following.

The third group, the Mild, contains thirty-seven

cases, all of whom recovered. The amount of indigo present in the urine on admission was practically the same as in the previous group, ranging between " $\frac{1}{2}$ " and "6" and averaging "1.9" as against "2". As noted in the two previous groups, the indigo shewed the same tendency to return to normal at the end of the first week. Apart from those in which a secondary disease appeared, four cases developed complications.

CASE 107 - E. R., male, $2\frac{1}{2}$ years.

On the 14th day of illness this patient developed otorrhoea: the indigo which had been standing at "1" increased to "3" and "4" on the two days previous to the discharge, making its appearance: when the latter occurred, it (the indigo) diminished to "2", and became normal the following day.

CASE 108 - M. McL., female, 4 years.

On the 30th day of her illness this patient's cervical glands became enlarged and for the following week her temperature fluctuated between normal and 102.8° F. The indigo increased to "2" from normal the day before, and to "3" on the day the adenitis developed: during the next week it ranged between " $\frac{1}{2}$ " and "6", and it fell to normal with the temperature.

CASE 109 - H. S., male, 5 years.

This patient's cervical glands became enlarged on the 17th day of illness. The indigo, previously normal, increased to "3" the day before the enlargement was noted, stood at the same level the following day, and then on successive days was "2" and "1", afterwards remaining at the normal level.

CASE 110 - M. F., male, 5 years

On the 47th day of illness this patient, while he

was going about, developed a secondary sore throat: membrane appeared on the tonsils three days later. The indigo increased to "4" and "8" on the two days previous to the development of the angina, and then slowly diminished, to become normal four days later.

H. ERYSIPELAS

In this disease a similar subdivision has been employed, viz:- Severe, Medium and Mild; the Severe group comprises those cases with a temperature of over 102° F. on admission: the medium, those cases with a temperature between 100° F. and 102° F. (latter inclusive) and the Mild all the cases with a temperature of 100° F. or below it.

The first group, the Severe, contains twenty cases, of whom one died. Specimens of urine were obtained from all the cases within twelve hours of admission. The amount of indigo present averaged "2" and varied between "1" and "5", though frequently during the course of the disease an increase to "6" was noted. The amount of indigo present remained raised as long as fever persisted, but diminished as the temperature returned to normal, remaining at "½" or "1" during convalescence.

CASE 120 - In the case which died, Mrs McM, aged 55 years, the condition was complicated by marked hypostatic congestion of the lungs, from the effects of which she died sixteen days after admission. Though the amount of indigo in the first two specimens examined was low, it rose to "2" on the third day of residence in the Hospital, and from that time until her death, thirteen

days later, the amount fluctuated between "2" and "6".

In four of the cases a recurrence was noted.

CASE 121 - J. McA., male, 39 years.

In this case the secondary attack made its appearance on the 7th day of illness, after the temperature had been normal for two days. The temperature rose to 101° F. and fluctuated between that level and 98° F. for five days, when it again became normal. The amount of indigo increased from " $\frac{1}{2}$ " to "2" on the same day as the rise of temperature was noted and continued at that level during the course of the pyrexia, on the subsidence of which it again became normal (see Chart IV).

CASE 122 - G. N., female, 15 years.

On the 10th day of her illness, this patient developed a secondary attack. The temperature had been normal for five days, but then rose to 101° F. and the following day to 104° F., returning again to 98.4° F. two days later. The amount of indigo was raised from " $\frac{1}{2}$ " to "2" synchronously with the rise of temperature, increased to "6" the following day, and returned to " $\frac{1}{2}$ " again on the subsidence of the fever.

CASE 123 - R. C., female, 26 years.

This patient, on the 18th day after admission, developed a mild secondary attack. The temperature rose to 100.4° F. and the following day to 103° F: it then returned to normal. With the onset of the pyrexia the indigo increased from " $\frac{1}{2}$ " to "1", and to "3" on the day of maximum temperature. It then returned to the normal level.

CASE 124 - W. S., male, 59 years.

This patient developed two mild subsequent attacks

on his 15th and 21st days of illness respectively. In each instance the temperature rose to 102° F. on the first day and to 103° F. on the following day, after which it became normal: the indigo likewise increased from "½" to "2" in each case during the two days of pyrexia, after which it became normal.

The second group, the Medium, contains seventeen cases, all of whom recovered. Specimens of urine were obtained from all the cases within twelve hours of admission, the amount of indigo being slightly lower than in the preceding group, averaging "1.6" as against "2". Neither did it range as high, varying between "1" and "3", while the duration of the fever continued over a shorter period.

In two of the cases complications occurred - a recurrence in one and in the other enlarged glands.

CASE 125 - E. McG., male, 73 years, developed a secondary attack on his 25th day of illness. His temperature rose to 103° F., stood at 99.6° F. the following day, and the next day became normal. The indigo increased from "1" to "2" on the first day of the recurrence and to "4" on the second day, becoming normal with the temperature the following morning.

CASE 126 - M. B., female, 17 years.

This patient developed enlarged cervical glands on her 23rd day of illness. Her temperature rose to 99.2° F. for two days, and the indigo increased from "1" to "3" on the first day, and stood at "2" next day, becoming normal with the temperature a day later.

The third group, the Mild, contains thirty-four cases, all of whom recovered. With the exception of one case, specimens of urine were obtained from all within twelve hours: the amount of indigo averaged

"1.4" and varied between "3" and normal, except in one instance which shewed "6" on admission, but in this case the disease was complicated by a septic condition of the scalp.

Complications occurred in three of the cases.

CASE 127 - Mrs M., female, 46 years.

This patient developed sub-acute Rheumatic fever with pains in her ankles, knees and elbows, four days after admission. Her temperature fluctuated between 99° F. and 101° F. for ten days and during this time the indigo varied between "1" and "3", becoming normal again on the subsidence of the pyrexia.

CASE 128 - W. C., male, 43 years.

This patient had a slight secondary attack on the 10th day of illness, which subsided again two days later. There was no rise of temperature, but his indigo increased from " $\frac{1}{2}$ " to "4" on the day the disease recurred, and stood at "2" the next day, after which it continued its normal course.

CASE 129 - Mrs J. S., aged 60 years.

Twenty-seven days after admission, this patient developed a sore throat, and during the four subsequent days the temperature ran between 99° F. and 101.2° F. The indigo fluctuated between "1" and "5" throughout the pyrexia, becoming normal again when the temperature subsided.

CONCLUSIONS

- I Indigo is always present to excess in the urine as early in the course of the fever as the case comes under observation: if an inference can be drawn from the few cases who developed a secondary disease during residence in Hospital, it is present from the onset of the period of invasion, and probably during the latter portion of the period of incubation.
- II Its intensity continues marked during the period of high pyrexia and gradually diminishes with the lysis of the fever. That this has some relation at least to the temperature is borne out by the fact that its disappearance corresponds very closely with the subsidence of the fever.
- III It is apparently closely related to intestinal disturbance and is therefore present in more marked amount in diseases of the digestive tract: this system is more likely to be upset in children, among whom an excessive amount is more frequently seen.
- IV It is also related to albuminous putrefaction occurring within the body, as shewn by its being present to excess during the process of suppuration.
- V Its presence in the urine probably means that products of putrefaction are circulating in the blood and in the tissues of the body, and are having a deleterious effect either by themselves or by their associated toxins.

VI By testing regularly for its presence, an excess of indigo in the urine may be of prognostic significance, at least in toxic cases.

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