THE DIAZO-REACTION IN PULMONARY TUBERCULOSIS.

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It has been routine practice to examine the urine of all patients admitted to the Victoria Hospital for Consumption, Edinburgh, during the past eleven months. Thereafter, each patient's urine has been examined at least nine times during his stay here, making a total of ten examinations for the reaction of the urine of each patient.

The diazo-reaction was first described by Ehrlich in 1882 as a test in relation to typhoid fever. In the course of his article he mentioned certain other diseases in which the reaction may also be sometimes obtained, such as tuberculosis and measles. Since the appearance of Ehrlich's article a great number of observations have been published, and most observers have directed their attention chiefly to the value of the reaction as a test in typhoid fever; a number, however, have studied the occurrence of the reaction in pulmonary tuberculosis. It is entirely in relation to pulmonary tuberculosis that the present observations have been made.

The opinions as to the value of the test in this disease have been widely divergent, and I trust that the results to be recorded may contribute a little towards the determination of the significance of the diazo-reaction in pulmonary tuberculosis.

THE REACTION

This seems to depend upon the fact that if sulphanilic acid (amido-sulpho-benzol) be acted upon by nitrous acid there is formed a substance, diazo-sulpho-benzol, which, if certain aromatic substances be present in the urine, will unite with them to form aniline colours.

The Reagents.

1. A saturated solution of sulphanilic acid in 5 per cent. solution of hydrochloric acid.
2. A $\frac{1}{2}$ per cent. solution of sodium nitrite.
3. Solution of ammonia.

Method.

1. To a small quantity of urine in a test tube an equal quantity of the sulphanilic solution—40 c.cm. is convenient—is added, and then a minute amount of the sodium nitrite solution—1 c.cm. is quite sufficient for the quantity mentioned—and the whole is now well mixed. At this stage the contents of the test tube may become of a well-marked yellow colour.

2. Next comes the important and characteristic part of the test. On adding sufficient ammonia to make the solution thoroughly alkaline, the urine becomes of a port-wine colour. It should be well shaken, when the foam will appear of a rose-red colour, the urine remaining of a port-wine hue. Some observers prefer to add the ammonia by means of a pipette down the side of the test tube, when a red-brown ring will be seen at the junction of the two. The urine is thereafter shaken up in the manner described.

3. If the urine be put aside now for twenty-four hours a sediment of a greenish colour may be obtained. This part of the test, however, seems of much less importance.

Cautions.

1. The urine should be as fresh as possible, and the reagents—sulphanilic and sodium nitrite solutions—be newly prepared.
2. Care must be taken to avoid adding too much of the sodium nitrite solution, as otherwise a pseudo-reaction may be obtained.
3. After the addition of the various reagents, if the reaction be present the urine becomes of a port-wine colour, and when shaken up the resulting foam is rose-red. The colour is most characteristic. In urines in which the reaction is not present the colour may be of various degrees of brown but not port wine, and the resulting foam is yellow but not rose-red. Failure to pay sufficient attention to the exact colour has doubtless been a source of error in some observations.

THE VALUE OF THE TEST IN PULMONARY TUBERCULOSIS.

Ehrlich, the discoverer of the reaction, while writing chiefly on its value in typhoid fever, mentions in the course of his article that he considers the occurrence of the reaction in tuberculosis to be of great import. Friedenwald considers that in phthisis the persistence of the reaction for two or more months justifies a gloomy prognosis. A. Blad and P. Videbeck are of the opinion that, in general, the reaction is negative in cases which clinically appear favourable, or, if positive, is weak and inconstant. On the other hand, it was found positive and strongly, or fairly strongly, marked with remarkable regularity in bad cases. In several instances, however, the positive result could not be obtained on the last days preceding death. Michaelis finds that the reaction is of value as a prognostic indication, in cases of pulmonary tubercle, and that when the reaction is present it renders the prognosis grave. From a large number of observations made on phthisical patients he has found that in 167

cases of the disease 111 gave a positive diazo-reaction, and 56 gave no reaction. Of the latter class 5 patients were cured, 43 improved, 5 were unchanged, and 3 died. In the group of cases which gave the reaction the mortality was greater and the improvement smaller. Thus of 111 patients 30 died, 13 gave not improved, and 15 were improved; while none were cured. Lorentz, of the Halila Sanatorium, agrees with Michaelis's opinion as to the value of the test in pulmonary tuberculosis. Nissen, in his observations on 462 cases of children suffering from various diseases, finds that in a case of chronic lung disease, in which the question of tuberculosis arises, the persistent presence of the reaction is in favour of the diagnosis of tuberculosis. He considers that the more constant its presence, the more acute and extensive the tuberculous process in progress. Bolli, whose observations extended to cases of pleurisy and peritonitis, besides phthisis, found that of 15 cases of pulmonary tubercle, those in the second and third stage, with the exception of 2, constantly gave a positive result to the test; if present in the early stage it is not necessarily of bad import; in the latter stages its absence indicates a somewhat less rapid course.

H. W. Syers, in the course of an article on the Diazo-reaction as a Method of Diagnosis in Clinical Medicine, states:

My experience of the diazo-reaction in phthisis is not large, but I have had the opportunity of applying the test in very advanced cases of the disease. My results do not in any way agree with those which would make the diazo-reaction either as of usual occurrence in the later phases of the malady, or, when it does occur, as being of any special significance. In ordinary cases of this description the result was negative, and when the reaction was positive there was no reason whatever to suppose that the case afforded any special feature of gravity beyond that which is normal at the stage at which the affection had arrived.

RESULTS OBTAINED AT THE VICTORIA HOSPITAL FOR CONSUMPTION, EDINBURGH.

The cases that have come under observation number 130, and these may be divided into two groups:

GROUP I.

Cases in which at least ten examinations of each urine were made during the course of the patient's residence, extending over a considerable time, weeks to months. These number 100.

The diazo-reaction was present in 16 and absent in 84. These cases may be considered further in relation to (A) temperature, and (B) the state of physical signs.

A. In relation to temperature, the cases may be divided into two sets:

1. Cases showing no pyrexia, or at most slight occasional rises of temperature.
2. Cases showing definite pyrexia.

The results are seen in the following table:

TABLE I.

Class.	No.	Positive.	Negative.
Apyrexic... ..	72	1	71
Pyrexia	28	15	13
Totals	100	16	84

It will be noticed that, of the 16 cases which gave a positive result, no fewer than 15 of these showed definite pyrexia. Moreover, the single apyrexic case which gave a positive result only did so on two out of ten occasions.

B. In relation to the physical signs, the cases may be divided into three types:

- (a) Cases showing bilateral consolidation, chiefly of apices, with few accompaniments.
- (b) Cases showing bilateral consolidation, but considerably more extensive than in first type, with a larger amount of accompaniments, and possibly few small vomicae.
- (c) Cases showing very extensive bilateral consolidation, with abundant consonating crepitation and large vomicae.

The results are seen in the following table:

TABLE II.

Type.	Number.	Positive.	Negative.
a	18	0	18
b	48	0	48
c	34	16	18
Totals	100	16	84

Of the 16 cases which gave a positive result, all, without exception, have occurred in type (c)—that is, at an advanced stage. The details of these 16 cases are interesting, and for purposes of description they may be divided into four groups:

1. This numbers 10 cases, and the reaction was positive on every examination. All these cases are now dead. The interval which elapsed between the discovery of the reaction in their urines and the date of death averages four months.

2. This includes 3 cases in which the reaction was at first negative, but subsequently became positive. These patients, also, have all died since these observations were made on them. In their case the appearance of the reaction preceded the occurrence of the graver physical signs, and was of much service by affording a warning as to the change for the worse which the case had undergone.

3. This includes one case of great interest:

Case 1.

On admission this patient had a definite reaction, and presented grave physical signs. Besides extensive bilateral disease of the lungs he suffered much from diarrhoea, passing albumen in his urine (2 gr. to the oz), and had a horrid stinking large fistula-in-ano, and a violently swinging temperature. He had been for six months in a large general hospital, and, though receiving every attention possible, did not mend in any way. The fistula, which had been operated upon whilst at the General Hospital, had obstinately refused to heal. It was little wonder that a gloomy view was taken as regarded the prognosis. However, after a few weeks, it seemed possible that this view should be disagreeably disappointed. The patient began to improve in every way, gaining weight, temperature swinging less, diarrhoea stopped, the fistula fast cleaning up and beginning to heal, whilst the diazo-reaction disappeared. He continued to improve thus for several months, slowly but surely making headway, the fistula healing almost completely. Notwithstanding this, about the nineteenth week of his residence here the diazo-reaction once more appeared, arousing fresh anxiety, which was unhappily justified by subsequent events. Some days later several anal abscesses appeared, terminating in fistulae, and the lung condition became urgent. The diarrhoea, which had been absent for several months, reappeared, and the patient became once again gravely ill.

4. This includes two cases, both of great interest. In both the reaction was at first obtained, and the patients' condition seemed serious. In both the reaction subsequently disappeared, and the patients' health immensely improved.

Case 2.

D. B., aged 25, carpenter, height 5 ft. 7½ in., weight 8 st. 4 lb., admitted April 2nd, 1902, suffering from very extensive bilateral disease, large vomicae and abundant consonating crepitation in both lungs, much expectoration, severe cough, night sweats heavy, haemoptysis frequent, liver enlarged 1½, tuberculous laryngitis, temperature swinging violently, pulse 90 to 100 (very small and feeble), very dusky and ill-looking, tubercle bacilli almost a pure culture, diazo-reaction very pronounced.

Further Progress.—August 1st, 1902. Physical signs vastly improved, cavities drying up rapidly, cough and expectoration very much less, night sweats nil, haemoptysis nil, temperature strictly natural (as tested every four hours), pulse 80 (tension and volume good), tubercle bacilli considerably less, patient's colour excellent ruddy look of health. He is very much stronger, and has gained 30 lb. in weight; no trace of the diazo-reaction to be found. The urine of this case was examined carefully and frequently. About a month after admission it was easily noticed that the reaction was very much fainter; some weeks after admission it completely disappeared, and has not returned. The disappearance of the reaction went hand in hand with the improvement of the patient, especially accompanying the gradual return of the temperature to the normal.

Case 3.

J. C., aged 31, compositor, admitted on April 15th, 1902. Height 5 ft. 10½ in., weight 8 st. 11½ lb., suffering from extensive bilateral disease. Right lung showed evidence of extensive vomica formation, and presented much crepitation elsewhere; severe cough; great weakness; haemoptysis on several occasions; pulse 100-110, small and very feeble; pallor marked; tubercle bacilli considerable; temperature occasionally rises slightly above normal; diazo-reaction slight but definite.

Subsequent Progress.—August 1st, 1902. Physical signs have immensely improved; crepitation very much less and of much drier quality; haemoptysis nil; cough slight; feels very much stronger. Pulse 80-90, tension and volume good; splendid ruddy colour; tubercle bacilli very few; temperature strictly natural, as per four-hourly chart. Has gained 18 lb. in weight; no trace of the diazo-reaction to be discovered. In this case the reaction disappeared much sooner than in the former one. Here also

the disappearance of the reaction coincided with the improvement of the patient's health. This case recovered more rapidly than the last, and it was impossible to obtain the reaction after three weeks from admission.

GROUP II.

Cases whose stay in the hospital have been of too limited duration to permit of more than one or two examinations of their urine at suitable intervals; these number 30.

If the classifications as regards temperature and physical signs be borne in mind, the results will be seen in the following tables. These cases, however, have been admitted too recently to permit of much observation, but corroborate my results obtained with the group of 100 cases.

TABLE III.

Class.	Number.	Positive.	Negative.
Apyrexia... ..	25	0	25
Pyrexia	5	2	3
Totals	30	2	28

TABLE IV.

Type.	Number.	Positive.	Negative.
a	5	0	5
b	16	0	16
c	9	2	7
Totals	30	2	28

It will again be noticed that the only positive results (two) obtained occurred in cases showing well-marked pyrexia, and with very extensive bilateral disease.

CONCLUSIONS.

From the observations recorded the following statements seem justified:

1. The diazo-reaction occurs in a comparatively small number of cases of pulmonary tuberculosis (18 out of 130 cases).

2. When present it is usually in cases with definite pyrexia (of 18 positive cases only 1 exception).

3. It is associated with an advanced stage of the disease.

4. Whilst present in a large proportion of the very advanced stages of the disease, it is absent in a considerable number of such cases. Thus in Tables II and IV, of 43 cases altogether of type c, the result was positive in 18 and negative in 25. Moreover, I may add that I have been enabled to examine several of these negative urines a very short time before the death of some of these patients, and yet it was impossible to obtain a positive result.

From the above statements it will appear that my views differ considerably from those of other observers. Bolli, for example, claims to have found the reaction in a very large percentage of his cases, and those in the "second" and "third" stages with the exception of two "constantly" gave a positive result, and what seems surprising is that he obtained the reaction in "early cases" when the reaction "is not necessarily" of bad import. I venture to think that failure to pay sufficient attention to details necessary in applying the test has been the cause of the widely divergent results recorded by different observers.

Among those observers who recognize the presence of the reaction as an indication of gravity, Michaelis draws attention to the value of the test, especially from the prognostic standpoint, and with his results my observations agree. Of 16 positive results among the 100 cases just reported no fewer than 13 of these are dead, 1 is dying, and the remaining 2 are very much improved. On the other hand, of the 18 very advanced cases that were negative only 4 have died, 8 improved and continue to do so, whilst the remaining 6 are much improved. It is hardly advisable to speak of cure, for

the time that has elapsed since the patients have been under observation is too short. That such advanced cases do recover is well known to those familiar with the disease. I may recall that last February, at the meeting of the Edinburgh Branch of the British Medical Association, at the Royal Infirmary, Edinburgh, 6 cases of recovery from very advanced disease were shown by Dr. R. W. Philip, as illustrative of this fact. Since then, at Dr. Philip's request, I have continued to observe carefully the subsequent progress of these cases. It has been most satisfactory in every way. Some returned to work shortly after; and, notwithstanding, have continuously gained ground. One patient, who has remained in the hospital to the present time, has gained a further 33 lb. since the meeting referred to, when he had already gained 37, making a total gain of 70 lb. from the time he first came under treatment in November, 1901. It is of special interest that these 6 cases, although gravely ill so far as symptoms, physical signs, and constitutional disturbances were concerned, gave a negative result. It is accordingly in such very advanced cases that the diazo-reaction would seem to be of particular service as an aid in prognosis. It affords a supplemental test of considerable value in discriminating prognostically between cases that in other respects seem equally serious.

Whilst the presence of the reaction is to be regarded as of grave significance, especially if it persists for any time, on the other hand its disappearance must be regarded as a distinctly happy omen.

Before concluding, I desire to acknowledge my indebtedness to Dr. R. W. Philip for much encouragement and help in the record of these observations.

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TWO CASES OF HYPERPYREXIA, WITH RECOVERY.

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THE first of the two following cases appears worthy of record because of the difficulties of differential diagnosis arising during its progress, and also because of the unexpected favourable result, while the second presents some interesting points of contrast to the first.

CASE I.

Mr. J., aged 32, clergyman, of neurotic type and family, had been staying in Colwyn Bay for several weeks, but had been to Manchester twice during that time, the last occasion being on October 1st. During the night of October 3rd he had a severe "bilious attack," with violent headache, pain in the legs, drenching sweats, and vomiting. I was called to see him on the next morning, when his temperature was 101° and his pulse and respirations 100 and 16 respectively. He had the aspect of a case of severe influenza, being much depressed and bathed in profuse offensive sweat. The tongue was large and indented, and covered with a thick creamy fur. There were no symptoms or signs of throat, abdominal, or lung mischief. At the junction of the two upper thirds of the outer side of the right humerus there was present a hard bony node of about the size of half a tangerine orange, which was very slightly tender to pressure or forcible percussion, and showed no signs of active inflammation. For this he had been attended for eight or nine weeks by Dr. Leslie Jones, of Manchester, who kindly informed me later that when first seen there had been an extensive periostitis implicating a large part of the deltoid and biceps muscles, but that under treatment it had steadily decreased in size. The case was regarded as influenzal, and an aperient and a diaphoretic ordered.

From the third to the fifth day no great alteration occurred, except that the patient's condition gradually became more serious. He was delirious and sleepless at night and profoundly apathetic, lying curled up under large quantities of

bedclothes, with his eyes half closed. Profuse sudamina appeared on the third day, and were followed on the fourth by a mottled rash, which consisted of a purple zone at the base of each small vesicle of the sudaminal rash. There were no physical signs in any of his organs, no albumen, sugar, or diazo-reaction in the urine, and no alteration in the periosteal node. The spleen was not enlarged.

On the sixth day the patient was obviously worse, the morning temperature had risen, and there was very slight (and doubtful) enlargement of the spleen. At 2.30 p.m., after sitting up to take a drink of tea, he suddenly exclaimed that he was dying, and fell back in a convulsion. I saw him within ten minutes, and he was then deeply comatose, there being at first a slight general convulsion, passing rapidly into absolute flaccidity of all the muscles. The pupils were widely dilated, and the heart was beating at 160, at first forcibly, and then weakly. The mercury of the thermometer placed in the axilla rose to a point corresponding to 111.5° . (The thermometer was sent to Kew on the next day, and certified correct to 0.2° up to 110° .) Strychnine sulph. gr. $\frac{1}{10}$ and a cold pack were given, the temperature dropping to 108° ; after which he was put into a cold bath, and kept there for about forty-five minutes, being taken out when his temperature had dropped to 101° , two more hypodermics of strychnine being administered during that time. While in the bath his pupils became less widely dilated, and his muscular tone to a slight extent returned. The sudamina entirely disappeared, and left only the purple mottling. After removal to bed a rectal injection of beef-tea and brandy was given, but this was immediately returned, and between 5 p.m. and 2 a.m. on the next day seventeen excessively foul motions were passed. During the evening he still remained relaxed and comatose, his temperature rose to 104° , and he appeared to be dying. A pint of normal saline solution, with half an ounce of brandy, was therefore injected subcutaneously, a convulsion occurring simultaneously. This was regarded as due to strychnine, of which he had now received gr. $\frac{1}{10}$.

Seventh day: At 3 a.m. the patient asked for a drink, and at 9.30 told me he had not felt so well for several days. His temperature (9.30) was 102.4° , the pulse 112 and of fair tension, and respirations 24. During this and the next day the rash changed in colour from a deep purple to a typical scarlatiniform one; and Dr. Leslie Jones, who saw him on the evening of the latter day, regarded the case as one of scarlet fever. Two or three small, sharply-defined punctae (apparently haemorrhagic) appeared on the right side of the palate, and persisted after the rash had disappeared. No further physical signs appeared, and there was no justifiable indication to chisel into the bony node. Blood taken on this day was negative as regards streptococci and Widal's reaction (Pathological Department, Owens College).

From the ninth to the fifteenth days the patient was