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EHRLICH'S DIAZO REACTION AS A DIFFERENTIAL-DIAGNOSTIC AID

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During my almost four years as chief physician of the Department of Internal and Infectious Diseases at one of the largest military garrison hospitals of our empire, I was in a position to perform Ehrlich's diazo reaction on many patients with many different diseases. This reaction was performed for the purpose of studying this interesting sickness symptom every time new patients were admitted with higher fever temperatures and a result always was recorded in all important cases, including the negative ones; I therefore now have a respectable volume of such results available which can be used for differential diagnosis.

The number of patients in whose urine the diazo reaction was performed in my department is more than 500 and the reaction itself was of course repeated several times or many times, depending upon the type of clinical picture so that there is also a possibility of arriving at a justified judgment with respect to the time of the start or end of the positive reaction in certain types of diseases.

In order to perform the reaction as quickly, as simply, and yet as accurately as possible, so that the entire operation will take hardly more than one minute, I arranged Ehrlich's directions as follows:

Into a measuring glass or a test tube marked for 12 g we pour 12 g of sulfanilic acid solution (Ac. sulfanilic. 5, Ac. mur. 50, Aq. 1000); to this we add 5 drops of a 0.5% sodium nitrosum solution. This mixture is enough for about 3 reactions and must always be prepared over again freshly.

Into a test tube we then put urine about 2 fingers high and we add the same volume of this mixture, plus 1 cm high ammonia and after that we shake strongly. The clinical reaction does not require any more accurate determination of the measure here because the results were entirely identical in many frequent repetitions. But while the same urine will always produce the same reaction, we rarely will find two different urines in the same color nuance of the diazo reaction. The gradations of wine-yellow, red-orange up

to deep purple-red, in the solution of purest white, lemon yellow all the way up to vermilion in the foam are very numerous. It is understandable that, for instance, a saturated fever urine will produce a more saturated color tone also in the diazo reaction than would the light-yellow urine of a healthy subject, without the aromatic urine components, which produce those reddish color tones, necessarily having to play a role here.

On the basis of the color shadings of the solution and the foam, I distinguished four types of reaction outcome:

1. Negative: wine-yellow to dark-ochre-yellow solution with white or lemon-yellow foam.

2. Weakly positive or neutral: solution dark-red with yellow reflex and reddish-yellow color tone in penetrating light, foam orange-yellow. Today I no longer call this reaction result "slightly positive" but rather "neutral" because, as I found in many cases, it cannot be used in diagnostic terms.

3. Positive: liquid dark vermilion with light-pink reflex [reflection] and identical color tone in penetrating light, foam reddish-white or pink. Neither the foam nor the reflection may have even the slightest shading in the yellow.

4. Strongly positive: purple-red liquid with ruby-red reflection and identical transparency, with nicely brick-red or vermilion foam (typhus reaction). These detailed statements concerning the color gradations of the diazo reaction appear necessary here only because we will refer to them several times later on and because this will avoid any further explanations.

The observations covered mostly the following forms of disease: abdominal typhus, measles, scarlet fever, dysentery, erysipelas, chronic and miliary tuberculosis, croupous pneumonia, pleurisy, pyemia and septicemia; it goes without saying that the diazo reaction was performed repeatedly in other diseases with fever, for instance, in rheumatism of the joints, in bronchial catarrhs, in malaria, angina, etc. The negative outcome in the latter cases was used in checking on the diagnosis and for the purpose of excluding other complications that might have been possible.

Abdominal typhus. The occurrence of the intensive diazo reaction in this disease has already been recognized as a main symptom of this disease and must occur during the first week, with such precision, that abdominal typhus is to be directly excluded if this reaction is absent. In my discussion of cases with a normal course, I will therefore confine myself only to this point: in all cases treated (31) the diazo reaction was highly positive and it remained just that, quite generally, until the start of the 4th week. In three cases, the diazo reaction developed only on the third day of the disease and in one case not until the 6th day of disease, even though the fever was almost 40° [C], which of course was a great obstacle in

coming up with a certain diagnosis. On the other hand, the switch in the diazo reaction from a highly positive to a negative or neutral result during the period of fever drop was often so sudden that one was quite surprised to note the still rather high fever in the evening. In one case involving a relapse after almost 14 days of apyrexia (standby reservist A. K.), there were once again highly positive diazo reactions with the new rise in the fever but this reaction then disappeared again after another 14 days, along with the drop in the fever. Because of the occurrence of the positive reaction failure, I immediately had to discard the diagnosis of a gastric disease, after the patient had felt so well for so long, and I had to assume a typhus relapse and at the same time order the patient to be put on a milk diet. The patient was discharged after recovery; in this case, the intestinal typhus had lasted more than 7 weeks.

In connection with the intensive diazo reaction, I believe I may mention one disease process which I found in the year 1900 under the diagnosis "Bronchitis purulenta." In addition to the catarrhal symptoms, spleen tumor and typhus tongue were found. The fever temperatures over 14 days were between 38 and 40° and gradually dropped from the third week onward. The patient was released as fit for duty after only 5 weeks in the hospital. Since a simple and purulent bronchial catarrh did not produce the diazo reaction, and since tuberculosis was impossible, I believe I am not wrong in assuming that typhoid fever was the cause of this positive diazo reaction.

At this point I might also mention a malaria case which revealed a positive diazo reaction. In the very many malaria cases, which we had particularly during the summer and autumn months, the diazo reaction was performed only in special cases and then this reaction was always negative, even in very intensive attacks; this was done because the patient's history as a rule led to the diagnosis and because the diagnosis was finally pinned down by temperature measurements and blood tests--these, by the way, were mostly relapses of a Febris intermittens acquired by these soldiers while they were on civilian status. The appearance of a nicely positive reaction in one doubtful case, which I think is worth describing briefly, was all the more astonishing here.

Hussar trooper A. T. was admitted on 29 September 1901 with the diagnosis "stomach catarrh with fever." In giving us his background history, the patient reported that he had been having stomach cramps, dizzy spells, and loss of appetite since 26 September and that he had fever daily, in the morning. The trooper was strong, moderately well fed, the tongue had a heavy coat, the chest organs were healthy, the spleen extended from the 7th rib to the rib arc. Temperature: 40.4°.

30 September, morning: temperature 37.4°, afternoon 36.7°, severe feeling of weakness.

1 October. Nighttime fever delirium. Morning temperature 39.5°. Diazo reaction positive. Afternoon temperature 39.4°. Therapy: morning

0.2 g calomel, afternoon, at 1600, 1 g quinine.

2 October. Pulse and temperature normal (A.M. 36.4°, P.M. 36.6°). Diazo reaction strongly positive. 0.2 g calomel three times per day. Evening 1 g quinine.

3 October. Temperature in the morning 39.6°, afternoon 39.4°, calomel.

4 October. Liquid stool with remnants of grapes with a very strong fetid odor. Morning temperature 36.0°, afternoon 36.6°; 1 g of quinine in the evening.

5 October. Morning temperature 37.4°, afternoon 38.4°.

6 October. Morning temperature 37°, afternoon 36.1°; since then, always below-normal temperature.

10 October. Patient feels well.

20 October. Patient discharged, fit for duty.

In spite of the pronounced tertian type of fever and the rapid and complete apyrexia, there were other symptoms present, in addition to the positive diazo reaction, which could simply not be explained on the basis of malaria. The patient's past history, the relative ineffectiveness of quinine, the absence of chills--all of these point to the fact that we were dealing here with Woodward's "Typho-malarial fever." Unfortunately, we were unable to process this case any further in clinical terms; the patient had to be treated at the time our hospital was at its busiest and medical and other aid personnel were replaced quickly.

The negative way in which the diazo reaction turned out in meningitis, which we will discuss later on, is very important, as we know, in the case of abdominal typhus, in terms of differential diagnosis. In some typhous diseases the cerebral irritation symptoms predominate in such a way, during the first week of the disease, that only a positive diazo reaction is decisive. But when this reaction--as we can see in the following case history--occurs also only on the 6th day of the disease and when, moreover, there has been a prior injury to the head, then the clinical picture of meningitis is complete.

Hussar trooper G. F. was admitted on 23 December 1902; he reported that 4 weeks earlier one of his buddies had accidently hit him on the head and that he had suffered a small but deep wound in the left crown region, where the scab was still visible. The day before yesterday, he had a pain in the left ear and he told us that he was quite deaf on that side. Otherwise he was quite healthy; yesterday he had chills, frequent headaches, and vomiting.

Status as of 24 December. Medium build, rather well-fed, temperature

39°, pulse 72. Pupils considerably constricted, weak reaction to light stimulus. Herpes facialis. White coat on tongue, tongue dry, patient sticks tongue toward the right side. Lung and heart normal, spleen not enlarged, abdomen bloated. Nausea, severe headaches, moaning, Sensorium free; diazo reaction negative, afternoon temperature 39.4°.

25 December. Patient vomited yesterday noon; nausea continues; patient complains that he cannot move his head forward. Muscle pains in the lower extremities. Diazo reaction negative. Temperature: noon 38.6°, afternoon 40.1°.

26 December. Patient is somnolent, complains of severe headaches. Pupils somewhat wider, sluggish reaction. No BM. Rigidity in neck and back. Diazo reaction negative. Noon temperature 39.7°, afternoon 39.6°, pulse 90.

27 December. Yesterday evening, solid stool. Ear report: much Cerumen, tympanic membrane somewhat clouded [darkened]. Headaches have decreased. Temperature at noon 39.6°, afternoon 40°.

28 December. Tip of tongue strawberry red, otherwise dry coat. Since yesterday noon, six BM's in the form of puree of peas. Ileocoecal region sensitive to pressure. Pupils react well. Spleen dullness somewhat enlarged. Diazo reaction positive, pulse dicrotic.--the further course was that of an abdominal typhus. Diazo reaction on 9 January negative for the first time, no more fever as of 15 January. The Widal test revealed good agglutination. Slow recovery with complete restoration of health. Patient discharged as fit for duty on 15 April.

In contrast, I would like to describe the following case which is characterized by the same diazo reaction in the beginning:

Supply sergeant G. G., admitted on 22 October 1902, reported that he had been having pains in his throat while swallowing since 19 October; at home he several times had chills with heat flashes and prespiration. Otherwise he had always been perfectly healthy until now.

Status as of 23 October: patient is strong, well nourished, skin pale, tongue heavily coated with flesh-red tip, throat formations highly inflammed. Over the lungs, a bright and full sound, widespread rough breathing. Spleen not enlarged, abdomen sensitive to pressure, somewhat meteoristic. Temperature at noon 39.6°, afternoon 40.1°. Diazo reaction heavily positive. Esbach positive, Indican increased. Blood test for plasmodia negative.

24 October: liquid stool of brownish color. Patient is feeble and very restless; patient has delirium, grasps and plucks with his hands constantly. Right pupil is definitely narrower than left pupil, both react well. Pulse reveals uneven frequency between 80 and 100. Temperature at noon 39.9°, afternoon 40.4°. Diazo reaction intensely positive.

25-27 October: deliria at temperatures of 40-41°; pulse rises up to 132, respiration up to 48 per minute; urine report same as on 23 October.

28 October: RHO, heavily increased rough breathing with much slimy-puny sputum, whose investigation for tuberculosis bacilli was negative. Blood: increase in white blood corpuscles.

30 October: stool like puree of pea; delirium continues until 1 November.

2 November: Widal's blood test positive. Right pupil remains narrower.

6 November: diazo reaction neutral. On abdomen, two roseola-like spots. Slow temperature drop; convalescence; patient discharged in best of health on 15 December with the same difference in the size of the pupils.

Measles. Among 9 cases I found the diazo reaction to be positive only 6 times and 3 cases were negative. But the latter were admitted for hospital treatment already with a pronounced exanthema and almost entirely or completely free of fever. In the positively reacting cases, it was found that the diazo reaction occurred even before the outbreak of the exanthema and that it disappears already after a few days, as the fever drops. In one child with measles--the child died of an accompanying catarrhal pneumonia--the diazo reaction was intensely positive on the 5th day of the exanthema.

Scarlet fever. We had a total of only 5 cases: in 3 of these cases the diazo reaction was negative and in one case it was highly positive; in one patient, who was delivered to the hospital in a dying state, it was impossible to make a urine test because the urine was discharged into the bed. The occurrence of the highly positive diazo reaction in that scarlet fever patient is of interest here because the long-lasting high fever of around 40° was accompanied by widespread, deep, gangrenous ulcers in the throat (diphtheria) which also led to suppuration of the throat glands. The microscopic study of the coat revealed the presence of numerous streptococci. This strange behavior of the diazo reaction toward scarlet fever must persuade us to consider that the abnormal urine products, which trigger the reaction, come not from the scarlet fever viruses but rather from the subsequent streptococci invasion, from the throat diphtheria. In the negatively reacting cases, the affection of the throat formations was confined only to superficial and minor symptoms.

In dysentery (8 cases) and erysipelas (37 cases), we never found a positive diazo reaction. The diazo reaction was negative also during the highest fever stage in one erysipelas patient in whom widespread phlegmons of the head and the neck with numerous metastases developed as a consequence; the patient died in this case.

Tuberculosis. The behavior of the diazo reaction toward this disease is rather strange. In 3 cases of miliary tuberculosis, which ended in death

accompanied by the symptoms of Meningitis basilaris, and whose diagnosis was confirmed by the obduction report, the diazo reaction came out negative: on the other hand, in those chronic-tubercular processes which were accompanied by lasting severe fever phenomenon, the diazo reaction was highly positive. This also includes 3 cases of Phthisis florida with widespread cavern formations and 6 cases of Tuberculosis serosarum, including 5 patients who were admitted with pleurisy, 2 of whom died of florid lung tuberculosis with lung abscess and pneumothorax and one case of Peritonitis tuberculosa. In many bacterioscopically established tuberculous lung processes with the usual evening fever and nighttime prespiration, the diazo reaction however was always negative. In other words, if we have lung tuberculosis, the positive diazo reaction points to a rapidly developing destruction action and therefore as a rule gives us an unfavorable prognosis. According to these observations, we are justified in assuming that it is not the Koch bacilli which produce those reactions in the urine that cause or trigger the diazo reaction, but rather other infection viruses, probably streptococci.

Pleuritis serosa and suppurativa; here we had a total of 83 cases and we never had a single positive diazo reaction although we frequently had a neutral one; the positive outcome of that reaction alone enabled us to assume a tuberculous form. The empyemas, which were treated operatively, finally ended with relative recovery.

Croupous pneumonia assumes a very special position of its own with respect to the diazo reaction. In 120 cases treated, the reaction was usually neutral (or slightly positive) and it was positive only in one case. Among the neutrally reacting cases, there were also very serious processes in which the critical or lytic temperature drop did not occur until the 14th-16th days. Of course, because of the favorable outcome of all pneumonia cases here, we have no observations on the behavior of the diazo reaction in processes that ended in death. The positive diazo reaction in the case of a pneumonia of the right lower lobe, which ended critically on the 11th day of the disease, is therefore all the more interesting: let me describe this case here briefly:

Hussar trooper J. K., admitted on 14 March 1901, reported that he had been suffering from fever, pains during breathing, headaches, and loss of appetite for 3 days. The afternoon temperature was 38.8°.

Status as of 15 March. Patient was well nourished, tongue was covered. RHU dullness with bronchial-like accentuated breathing and fine-bubble rattling. Spleen dullness not enlarged, abdomen not bloated. Temperature at noon 39.9° and afternoon 40.1°.

16 March: temperature at noon 40.5°: afternoon 38.1°, after [administration of] 1 g Phenacetin: no sputum.

17 March: subject is well-being; tongue very dry, crusty with flesh-

red edges, severe ileococcal gurgling. Spleen dullness not enlarged. Diazo reaction slightly positive. Temperature at noon 38.9°, afternoon 39.2°.

18 March: no change in condition; temperature at noon 39.9°, afternoon 39°.

19 March: diazo reaction intensely positive. Rough breathing spread over the lungs, with dry rattling noises, sputum catarrhal-slimy. Patient is somnolent. Temperature at noon 39.1°, afternoon 39.8°. Calomel 0.2, 3 times.

20 March: edge of spleen palpable during deep inspirations, dullness not enlarged. Temperature at noon 38.8°, afternoon 38.1°.

21 March: critical temperature dropped down to 35°, pulse weak, 68. General condition good. Temperature continues to remain low. Discharged on 10 April as fit for duty.

With respect to the abnormal course of this disease process we would not be wrong in interpreting the latter as a pneumotyphus because of the positive diazo reaction, in other words, it would not be a Pneumonia adynamica which would have given us a neutral diazo reaction here.

Pyemia. In four pyemic processes observed here, the diazo reaction was negative. I would like to sketch these interesting cases briefly:

Gunner first class S. W., admitted on 9 December 1899 with daily recurring fever, with temperatures around 40° accompanied by morning remissions of 36-37°. Spleen tumor. Quinine. No fever, good condition at the end of December. Was scheduled for discharge on 4 January but chills developed again on the same day and came back daily, in the afternoon. Diazo reaction negative. Blood test reveals increase in white blood corpuscles, gigantoblasts, nucleus-containing red blood corpuscles. Rapid decline. On 1 February 1900: death. Obduction report: Abscessi multiplicati hepatis.

Hussar trooper E. K. N., admitted on 26 January 1901 with Pneumonia crouposa biliosa (of the right middle and lower and then the left lower lobe) with lytic drop on the 14th day of the disease. On 9 February, several boils on the trunk. After these boils were opened, new boils kept coming up, accompanied by rising fever; later on there were numerous pus foci in the subcutaneous tissue. Until 29 March, several of these boils were opened daily under the skin of the trunk and the metastases under the skin of the extremities; we had a total of more than 100 boils; from these, a large volume of thick, yellowish pus was removed. Diazo reaction neutral. Recovery; discharged on 25 May 1901 in the best of health and good nutritional state. Staphylococcus pyogenes was established microscopically in the pus.

Rifleman P. K., admitted on 10 October 1901 with erys[illegible] of the face. After 14-days serious development of erysipelas and sev[illegible]ays of

complete apyrexia, tumors began to fluctuate under the skin on the skull; these tumors were opened and large volumes of thick pus were removed. Accompanied by moderate fever, new large abscesses developed under the scalp, on the back of the neck, at the upper extremities and in the hip region. Operative treatment. Good condition and fever drop; 4 weeks after end of erysipelas, erysipelas of the face suddenly came back, accompanied by severe fever the patient, now in very bad physical condition, died of this new development on 25 November. The diazo reaction was always negative.

In a 4th case of a pyemic disease, that is to say, Osteomyelitis with Coxitis suppurativa, which I was able to observe only during the initial stages, I repeatedly performed the diazo reaction which came out negative each time. In the pus of this patient, we were able to establish Staphylococcus pyogenes microscopically; during the breeding process, these were identified as Staphylococcus pyogenes albus.

Septicemia: here we had two cases in which the diazo reaction came out positive from the very first day of observation onward. Both cases are interesting from a differential diagnosis viewpoint because the points of entry for the sepsis were quite insignificant and because we had to make a decision here between the latter and phthisis, respectively, pneumonia. Croupous and lobular pneumonia give us negative or neutral diazo reaction; this is why the positive diazo reaction here alone could be evaluated as decisive; phthisis, on the other hand, likewise reveals a positive diazo reaction but only in the advanced stage, where it points to pathological phenomena on the lungs and the serous membranes which are clearly observable on the basis of the physical findings. It is obvious that abdominal typhus and the measles must be ruled out from the very beginning. For both of these case histories, I would like to present the initial symptoms which are significant to the determination of the diagnosis.

Standby reservist J. H., recalled for maneuvers, was admitted to the hospital on 17 October 1902 for observation of an earache and the report stated the following: "Chronically-pusy middle-ear infection with tympanic membrane defect"; on 19 October, the patient was transferred to my department because of high fever, blood-coughing, nighttime prespiration, and consumptive weakness. Patient reported that he had been coughing since 3 October and that he coughed blood during the preceding night.

Status upon admission: feeble, thin, cachectic appearance, tongue heavily coated, dry with flesh-red edges, clavicle pits deeply depressed. Bright and full sound over all of the lungs and normal lung boundaries. LHO increased, bronchial-like breathing with individual moist rattling noises, in the lower portions; rough breathing. Heart sound pure. Spleen dullness not enlarged. Temperature 37°, pulse 60. Nighttime vomiting of bilious-slimy masses. Patient complains of headaches. Diazo reaction positive. Afternoon temperature 37.4°.

21 October: temperature 39°, pulse 92. Sensorium somewhat benumbed,

region of right mastoid process painful. Diazo reaction heavily positive. No coughing, no expectoration. Afternoon temperature 38°.

22 October: chills at night; temperature 37.4°, pulse 84, afternoon temperature 39.5°. The expert investigation of the right ear revealed a minor separation, no symptoms of any disease of the petrous portion of the temporal bone. Corresponding treatment and bandaging. Sensorium free. Coughing with slimy expectoration.

23 October: great pain behind the Processus mastoideus. Temperature 39.1°. Icterus. Diagnosis: Septicemia (Sinus-thrombosis).

Here we might also note the positive diazo reaction while there was no fever at all on 20 October. We could therefore rule out abdominal typhus with almost complete certainty; with respect to the lung finding, we could assume sepsis with great probability on the basis of the diazo reaction, already on the first day of observation.

The following case history involves the differential diagnosis between septicemia and pneumonia and is important here because accidental pneumonias occur by no means infrequently during the healing of wounds. Because only lobar and lobular pneumonias do not produce any positive diazo reaction, such a reaction would then point to a septic lung affection.

Assistant gunner A. N. suffered a contusion of the right middle finger, with crushing of the second and third phalanx bones. Exarticulation on the same morning in the first Interphalangeal joint, antiseptic bandage, smooth wound healing. On 3 April, fever of 40° accompanied by pneumonia phenomena on the right lung.

Internal state: strong, well nourished, hollow sound along the lower parts of the lung, rough breathing there with numerous dry and moist rattling sounds, partly sounding on the right. Left coughing, minor expectoration with pure mucus. Temperature 38.5039.7°. Diazo reaction intensity positive, strong darkening of albumen during heat and acid test.

1-8 April: delirium, prostration, subicteric coloration. Temperature around 39°. Blood test: white blood count increased, in groups of up to 12; in blood plasma, individual groups of two or three connected streptococci. Diazo reaction always positive.

As we look over the overall results of these observations, we find a positive diazo reaction in the following diseases:

1. In abdominal typhus, in all cases (middle of the first to the end of the third week).

2. In measles: prior to eruption and during the initial stage of exanthema.

3. Scarlet fever diphtheria.

4. In advanced lung phthisis and Tuberculosis serosarum.

5. In Septicemia.

Apart from the two first-named diseases, the diazo reaction thus seems to be triggered in those diseases in which the streptococci enter the blood circulation and announce their sudden flooding through high (septic) fever. After the antistreptococci serum was successfully used in scarlet fever and recently also in connection with sepsis--because i.v. collargol injections also reveal favorable results in septic processes--we can say that the diazo reaction will furnish a welcome indicator for the early application of this therapy; it may well be the only indicator which offers us any chance of success in case of general affections.