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Arthur Bowles

University of Nebraska Medical Center

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TOXIC REACTIONS TO INTRAVENOUS ARSENICAL THERAPY
Their Early Manifestations, Prevention and
Treatment.

Arthur Bowles.
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TOXIC REACTIONS TO INTRAVENOUS ARSENICAL THERAPY.

Their Early Manifestations, Prevention and Treatment.

Toxic reactions to intravenous arsenical therapy are accidents, which in the light of present medical knowledge do happen disregardless of what is done to prevent them. The value of arsenic, however, is accepted and its evils are far overbalanced by its good effects, so that arsenic must be given a place in the therapeutic attack upon syphilis.

In this paper a review of recent literature, as well as a study of selected cases from the Dispensary of the College of Medicine of the University of Nebraska will be presented. This is done as an attempt at the formation of certain postulates which would aid in the early recognition of patients in whom arsenic, if continued, would produce serious reactions.

The theories as to the causation of these reactions are many and some of them quite bizarre. The physiology and chemistry underlying these reactions is by far too large and as yet too unsettled a field for the neophyte to attempt to cross and so will not be considered at all. We will merely try to show some of the clinical phases which have been covered and some material which has proven to be of practical value.

Arsenic has been used internally for centuries. It was recognized in 1857 by Devergie(1) who demonstrated that arsenic when taken internally would cause an eruption upon the skin. Arsenic used intravenously in the treatment of Syphilis dates from 1909 when Paul Ehrlich discovered the therapeutic effect of Salvarsan, which was used later in the treatment of human patients. He, called this drug Salvarsan,
and still later discovered another drug called *Neo salvarsan*, since which time other workers have demonstrated other preparations of arsenic the value of which are rated in various ways by different authors. Among these preparations are *Silver-Arsphenamine* and *Tryparsamide*, as well as *Sulfarsphenamine* and *Bismuth Arsphenamine sulphonate*.

Toxic arsenical reactions as they present themselves in the patient are many and varied. Classifications of them has been attempted by many writers. One of the recognized authorities(2) divides reactions as follows:

1. Immediate Reactions (during or immediately after injection)
   A. The acute physico hemoclasic reaction
   B. The acute vasoparetic or Nitritoid Crisis
      - Mild
      - Severe

2. Early Reactions (following within 24 hours after injection)
   A. Gastro-Intestinal reaction
   B. Protein colloidal shock reaction
   C. Accidents of injection

3. Late Reactions (occurring 1 or more days after injection)
   A. Hemorrhagic Encephalitis
   B. Dermatitis and allied reactions
   C. *Meningitis* neurorecurrences and neural Herkheimer reactions
   D. Jaundice.

This classification is good but bulky. Other writers(3) divide reactions into Immediate reactions and Delayed reactions. As in all classification, an adequate listing is almost impossible since the causes of toxic manifestations are multiple and the reactions may affect practically every part of the body. The reactions might be listed in a manner...
indicative of the organs they effect, namely, as cutaneous reactions and nervous reactions. But, flaws are very apparent in this classification also. The occurrence of toxic reactions in regard to frequency is most easily expressed as a percentage of patients treated. One clinic (4) gives an incidence of 11.2% of patients who had reactions out of a total of 2,100. Other figures are 15.3% (5) and in the United States Navy statistics of 1 reaction to 1077 intravenous injections of arsenic are reported. These figures include all reported reactions, some of which are not serious, but the Navy figures show a fatality ratio of 1 to 17,434 intravenous injections of arsenic over a 4 year period (7). Death occurred in 3.22% of the reactions seen at a one clinic (6). These figures show that toxic arsenical reactions are not frequent but that even with the utmost care they will occur and anything which can be done to avoid them would be merciful at least.

In any attempt to consider the etiology of arsenical reactions chaos is encountered. Theories have been advanced by all who have had the opportunity for observing any reactions. Since the causes apparently are at a variance (2) we will consider them under the various headings.

Considering the immediate reactions, if the effect of the injection of an acid solution of arsphenamine can be called a reaction it should be mentioned in this category. It's symptomatology is usually severe pain, choking, dyspnoea with signs of a pulmonary failure death. The signs of early toxic reaction are varied. Vomiting, quite a common reaction (6) is often unreported by the patient and its presence must be elicited by careful questioning. Injection of the conjunctiva and flushing of the face may occur. Other things noted are a generalized erythema various urticarial eruptions.
Nitritoid Crisis when present occurs immediately following injections. It is usually characterized by flushing of the face and dilatation of both pupils of both eyes. Its name is indicative of its symptomatology, since the name was given it because of its similarity to the effects noted from the inhalation of amyl nitrite. Coughing may be a pronounced symptom and it has been noted to have been so severe as to have been called an Acute Collapse. It's incidence is a problematical thing as it is usually not reported unless extremely severe, suffice it to say that Nitritoid Crisis occurs often. It's etiology is obscure. This reaction usually appears during the first course of arsenic but commonly after the patient has had several injections rather than after the first injection. It's severity is also subject to dispute, some authors stating that it is not a contraindication to further arsenic(8) and other men say that it is a contraindication(9) reporting cases where it has been followed by hemorrhagic disturbances.

The prevention of Nitritoid Crisis is a thing upon which much has been written. Certain facts about it are known however. The mental state of the patient if calm aids in the prevention of the reaction. Adrenalin usually will lessen the severity of the attack. Atropine by hypodermic will sometimes prevent the crisis. Some good results have been reported by the use of ephedrine by mouth preceding the injection. Possibly the vehicle which carries the medication may be changed to advantage. Normal saline(10), blood serum, calcium chloride and glucose have all been advocated, but the consensus of opinion favors glucose(13).

The treatment of Nitritoid Crisis is that of shock and is merely the support of the patient through the acute phase.

The early reactions which occur within twenty four hours after
injection are many. Probably the most frequent reaction is that of nausea, which may or may not be accompanied by vomiting, diarrhea, chills, fever, headache and other symptoms such as muscular pain.

Other symptoms reported in this time interval and usually accompanied by nausea are coughing, rheumatoid attacks and vertigo, which are usually of short duration and require only sedation and rest.

The prevention of these gastro-intestinal reactions is a problem. The time of injection in relation to the patients eating is an important factor, so that the so called timing, that is proper timing of injections, meaning that the patient should be prevented from eating for a period of time, before and after the injection(10). Other methods of avoiding this reaction is by the use of more dilute solutions(12), as well as the slower injection of the drug used.

The protein shock reactions also occur at this time and are characterized by headache, chills and fever. It's occurrence is not common or at least it is not recognized. These cases are considered by Cummer(12) as being in reality based upon the same pathology as hemorrhagic encephalitis, but in a much milder degree.

The accidents of injection, such as infiltration of the soft tissues and thrombosis are not considered in this paper.

Later reactions which occur within a period of time from twenty four hours to several months after injection are as a group more serious than the earlier reactions.

Hemorrhagic encephalitis is one of the most feared of the toxic reactions to arsenic. It's incidence is reported as occurring once in 17,434 injections of arsenic in the United States Navy by Phelps(7). Other writers state that it occurs in a small percentage of their cases and it is uniformly rated as having a high incidence of mortality. Milian in 1912, first described it and called it a serous apoplexy. This con-
dition is acute and it's pathology is that of multiple hemorrhages into the brain substance. It is characterized by a sudden onset with coma coming on quickly. Some patients have been found unconscious and have never regained consciousness. Convulsions, chills, vomiting and a hyperpyrexia are usual symptoms. The pressure of the cerebro-spinal fluid is always greatly increased. The course of the disease is uniformly short excepting in the rare case of recovery when six to eight weeks is usually required. Treatment is symptomatic, since Gray(14) states that sodium thiosulfate is of little value in these conditions. Repeated spinal drainage and hypertonic solution of glucose are advocated by Lingenfelter(8). As factors influencing the occurrence of hemorrhagic encephalitis, Cole (5) concluded that it is a disease of young adulthood and is seen early in the course of syphilis and also early in the course of treatment. Gray(14) thinks that the use of a heavy metal in concurrence with arsenic, probably predisposes to hemorrhagic encephalitis. Phelps(15) in a series of 18 deaths from acute hemorrhagic encephalitis found that the onset usually occurred, that is on the average, 74 hours after the injection, and he states that the majority of cases present no prodromal signs, but that most of the cases had large initial doses of arsenic.

The skin is a frequent site of the manifestations of toxic reactions to arsenic. Evidences of cutaneous pathology due to arsenical reaction are many in number.

The skin reactions may be divided into mild and severe.

One of the mild reactions is a transitory erythema usually on the chest and face. It subsides quickly and needs no treatment(6). It may or may not be accompanied by pruritis. Urticaria also often follows the injection of arsenic and may be similar to the Nitritoid Crisis. Herpes simplex and zoster are seen. Wolheim (16) thinks that herpes zoster is an indication of serious hypersensitiveness, demanding
immediate cessation of arsenic, however the condition usually requires no definite therapy.

The brightening and recurrence of a secondary syphilitic skin eruption during treatment is a manifestation of a Herxheimer reaction in the skin and indicates a need for intensive treatment. Stokes(9) noted that under arsenical treatment for syphilis several patients with fungus infection of the skin showed marked exacerbation of lesions on the feet. Pruritis may occur with no other findings(11) and when it does it must be regarded suspiciously as it may be the forerunner of a serious dermatitis.

The more severe skin reactions include the fine scarlatinial eruption which often is accompanied by mild constitutional symptoms and which frequently shows some desquamation even going on into an exfoliative dermatitis. Purpura simplex also has been noted when arsenic was being given(17). Diarrhea may be present as a result of an ulcerative colitis presumably on an arsenical basis.

The true exfoliative dermatitis caused by arsenic is a serious chronic disease with a generalized inflammation of the skin and exfoliation accompanied by secondary infection in most cases(18). Treatment is intravenous sodium thiosulfate and some local application such as potassium permanganate to prevent serious secondary infection.

Other skin manifestations may be similar in character to lichen planus(19). A permanent pigmentation of skin areas is reported by Diasio(16), which was persistent at the end of three years. Also rare cases of arsenical hyperkeratosis are noted. Skin reactions to silver-arsphenamine bring a new entity that of generalized argyria. Becker(21) says the drug is dangerous and a total dosage of over 15gm. is apt to be followed by argyria. Spiagel(22) puts the safe dosage (total) at 8 gm. while Cannon(23) used silver-arsphenamine never the less with no untoward effects.
Jaundice as a result of the toxic action of arsenic is an entity which at the present time is quite unsettled. It may occur without any other symptoms or findings, while it is also found in combination with nearly all the toxic reactions. When jaundice occurs the question which must be answered is "What is the cause of the jaundice?" as it may be due to arsenic, it may be due to syphilitic infection of the liver, it may be due to some other infection, cholelithiasis, cholecystitis or it may be caused by a Herxheimer reaction. The best support of the theory that jaundice is related to arsenical absorption is the fact that jaundice is so much more frequent since the arsenicals have been used in the treatment of syphilis. Kolmer states that jaundice occurring in the primary and secondary stages of syphilis is practically always due to the syphilitis infection. Milian as quoted by Birnie says that jaundice appears two months after treatment and that it usually appears in the untreated cases. Certainly factors such as infection could occur, even in the face of arsenical irritation. O'Leary even states that possibly the arsenic lowers the liver resistance to infection.

At this time the functional test of liver capacity are of very little value, as are the examinations of various body excreta for arsenic.

The Herxheimer reaction in regard to the activation of a latent focus is mentioned by Ireland(10) and he stresses the fact that in every patient with a possibility of syphilis of any viscus a course of a heavy metal should precede arsenical therapy. Dosage according to Shoch(24) has little effect on liver damage. The sum of this material would seem to show that arsenical damage to the liver is to be diagnosed by elimination of other conditions.

The Mayo treatment(25) is duodenal lavage, sodium acid phosphate per os and sodium thiosulfate intravenously. In regard to sodium thiosulfate Surber(19) states that overdosage will liberate the stored
arsenic from the tissues too rapidly for it to be eliminated without causing some ill effect. He cites a case of exfoliative dermatitis which was complicated by icterus following massive thiosulfate therapy.

The incidence of jaundice is high and the infectious theory is given support by the fact that in some clinics it has appeared to have occurred in epidemics as it did during the World War(5).

The cases of transverse myelitis due to arsenical therapy are reported rarely and are subject to some discussion. They are characterized by severe headache and constitutional symptoms. Lindemulder(26) feels that these are closely allied with neurorecedives or neural Herxheimer reactions. This symptomatology may closely simulate an encephalitis and demands an accurate diagnosis since the treatment of the two conditions is exactly opposite. Polynearitis as a toxic reaction is late in a majority of cases and is preceded by prodromal signs of arsenical intolerance.

Another nervous manifestation is the retro-bulbar neuritis which is usually caused by the pentavalent Tryparsamide. It is manifest early by narrowing of the visual fields so that Potter(27)says that the visual fields should be taken before the course of treatment starts and also before each injection. Ireland also advises ophthalmic consultation.

Neurorecedives may occur in the early case with insufficient treatment and come on after an interval without treatment according to Rile(18) who thinks that the condition may affect any of the cranial nerves especially the auditory and oculomotor. It is a paresis of the nerve, rarely taking on an epileptiform character. Birnie(11) reports 4 cases which simulated Bell's palsy and occurred in primary syphilis with inadequate treatment.

Herxheimer reactions in general can be said to be due to some
disturbance of the established relation between the immunity of the host and the spirochetes. Most writers (4) feel that the arsenical therapy either releases some endotoxin as part of its spirochetocidal action or else the treatment activates some latent focus. A course of heavy metal is given as a prerequisite of arsenical treatment by Lindsay (15). Herxheimer reactions are not important if the disease is in an early stage but the later the disease the more dangerous they become.

The definite blood changes shown in certain toxic arsenical reactions are an interesting field. Their incidence as diagnosed entities is small but their occurrence is possibly more common than known. Stephens (17) feels that all the blood dyscrasias due to arsenical intoxication have as their most prominent feature a depression of bone marrow and bone marrow function.

The most innocent is purpura simplex which occurs a few hours after treatment and shows little change in the blood picture. Purpuric spots are subcutaneous and recovery is spontaneous. The condition is a definite contraindication to further arsenical therapy.

Purpura hemorrhagica presents the clinical picture seen in the disease when not related to arsenic. Platelets are always greatly reduced. Agranulocytic angina presents the same clinical picture as does the disease when not related to arsenic. The Aplastic Anemia found in arsenical intoxication is very severe. Hemorrhagic phenomena accompany the disease in its later stages. Death is uniform in this condition.

Bamforth (28) does not believe that there are any prodromal signs in the blood dyscrasias and found many cases complicated by jaundice. Lindsay (15) thinks the disease is apt to occur during the second course of treatments with arsenic and that usually there are some hemorrhagic signs indicating the condition which are disregarded. He feels that initial dosage is too high in the cases.
he has seen. Roberts(29) thinks that careful study of most toxic arsenical cases whatever the condition would show some damage to the hemopoetic system. Stephens(17) thinks that dosage and time have little to do with the condition and that arsenic depresses the bone marrow in every patient for an interval of 24 hours following an injection. He suggests an organ sensitivity as an etiological factor.

Among other conditions due to the toxic action of arsenic are kidney damage(25) affecting primarily the tubules and this condition is quite rare. Ireland(10) quotes Stokes as believing a reaction may be caused by impurities in the rubber tubing used in the gravity method of injecting arsphenamine.

A radical theory is advanced by Sequeria(30) that many dermatoses thought to be due to arsenic are really due to stimulation of the latent microbe infections and the scarletiniform rash and eruptions such as herpes are indications of inadequate treatment.

Cases taken from the Dispensary of the College of Medicine of the University of Nebraska are used in illustrating certain of the reactions mentioned.

I-White male, aged 41, #53882, entered the dispensary December 10th., 1931, with a history of a penile ulcer 6 months previously and a 4 plus blood Wassermann 4 months previously. He was seropositive on entrance and was given 1 intramuscular injection of bismuth and a course of 9 intravenous injections of neoarsphenamine receiving a treatment twice a week. The first injection was .25 gm., the second was .4 gm., and the remainder were .5gm., each. 4 days after the last injection he had an erythematous eruption on the chest, arms and shoulders with the subjective complaints of intense pruritis and tingling of his skin. Between Jan. 25, and March 17 he
was given 15 intravenous injections of Sodium Thiosulfate 2 grams each. During this interval his symptoms were gradually clearing and on March 24 he was symptom free, seronegative and a course of intramuscular bismuth was begun.

II-White female age 24 #53582 entered the dispensary Nov. 21, 1931 for a general physical examination presenting no complaints. She returned on Feb. 20 seropositive with the history of a generalized skin eruption during the third week in Jan., which had since disappeared. At that time she also had a sore throat and a clinical diagnosis of mucus patch was made. She was given 3 injections of neoarsphenamine 0.25 gm., and 0.4 gm., and 0.4 gm. On the fourth day after the last injection she was sent to the hospital. She had been nauseated and had vomited a few hours after her treatment, and the next day noted a generalized mottled multiform red eruption. 2 grams of sodium thiosulfate was given intravenously and in 24 hours the patient was symptom free. On her return to the dispensary she was started on a course of intramuscular bismuth.

III-White female age 28 #50591 entered the dispensary, February 14th., because of a diagnosis of congenital syphilis, in her two months old baby. She was seropositive and began a course of intravenous neoarsphenamine, she received 3 doses, the first was 0.15 gm and the next two were each 0.3 gm. One week after the third injection the patient stated that following her last treatment she was nauseated, vomited and had a chill, her temperature at that time was 102 and she had a generalized reddish eruption. She received five injections of sodium thiosulfate, each 2 gm, and then was given a course of intramuscular bismuth. On August 27th., she began a course of neoarsphenamine, receiving seven injections, the first 0.1 gm, the second 0.2 gm and five injections of 0.4 gm each.
Patient stated that she was nauseated after the next to the last injection and that after the very last injection, she was sick with a chill and fever. She was given no treatment for two months and then another course of neoarsphenamine was begun. The patient received nine injections of .25 gm each, with no signs of intolerance.

II-White male, age 36, #40746, entered the dispensary October 11th., with a penile lesion positive for treponema pallida, seronegative, received four injections of neoarsphenamine, returned one week after last injection with a marked jaundice, he was given seven injections of sodium thiosulfate of 1 gm. each. He was put on bismuth and one year later began a course of neoarsphenamine, each dose being .2 gm. which he tolerated with no trouble.

V-Negro male, aged 31, #25460, entered the dispensary on February 9th., with a genito-urinary complaint. The patient was seropositive. He received three injections of neoarsphenamine, each dose being .5 gm. and he complained of aching in his arms and legs. Individual doses were cut to .3 gm. he then was given a course of bismuth and on June 8th., he started another course of arsenic. Patient returned within twenty four hours after the first injection with an extensive purpura of both legs with slight itching. June 11th., purpura was greatly lessened and he was given .1 gm. neoarsphenamine. Patient received four injections of neoarsphenamine each dose being under .5 gm. but returned on July 2nd., with a moderate edema of both ankles. Urinalysis was negative, and he received two more injections of neoarsphenamine of .3 and .45 gms. respectively. He was then given a course of bismuth and on December 14th., he began another course of neoarsphenamine with maximum dosage of .5 gm. which was well tolerated.

VI-Negro female, age 29, #50149, entered dispensary January 8th., 1931,
with history of generalized eruption and genital lesion eight years ago, patient being seropositive. She was given three injections of neoarsphenamine of .25, .5 and .5 gms., respectively, and after last injection, she suffered, vomiting, fever, edema of both ankles and pruritus. She was then given 1 gm. sodiumthiosulfate and eight injections of bismuth. April 27th., she began the injections of neoarsphenamine, tolerating .5 gm., well. Since which time she has again been given bismuth, but is now on another course of neoarsphenamine tolerating .5 gm. with no untoward symptoms.

VII-White male, age 35, #48273, entered the dispensary August 10th., 1930, with a history of a seropositive reaction. Patient was still seropositive and so was given three injections of neoarsphenamine of .25, .5 and .5 gms., respectively, but came in with a fine scarlet generalized rash on second day following treatment. He was then given twelve injections of sodiumthiosulfate of 1 gm. each, since which time he has tolerated two courses of neoarsphenamine, nine injections of .5 gm. each and nine injections of .5 gm., with no trouble whatsoever.

These cases serve to illustrate a few of the conclusions given by the various authors. The first and second cases show rather severe dermatitis, which cleared under sodiumthiosulfate treatment and which occurred early in the disease with no prodromal symptoms and under small dosage.

The third case illustrates a gastrointestinal reaction which was severe and which recurred, but the untoward symptoms were managed very nicely, by the simple means of timing her injections and aiding her elimination. With no other change than that of better technique she has tolerated further arsenical therapy.

The fourth case with the asymptomatic icterus presents a picture of an icterus evidently on some other basis than arsenical liver damage.
The fifth case was a purpura simplex who later tolerated arsenic. This is in direct opposition to the tenets laid down by some authors. From an analytical standpoint it is too bad that blood studies were not made on this patient. The possibility would be that his blood would show some aplasia following each injection.

Cases six and seven show that after mild early reactions, arsenic is tolerated apparently, as one has a right to expect normally or rather in a standard manner. The last two cases, being six and seven, could be placed in the category of cases, who react either to the particular preparation or else the individual physical makeup of both patients varies from time to time.

Toxic reactions to arsenical therapy are varied and many of them are unusual, but in actual practice a knowledge of them becomes most valuable, only when we can prevent them or at least not have any serious reactions as a result of therapy. The choice of drug used, of course, is something upon which we have not touched. Suffice it to say, that arsphenamine and neoarsphenamine show about an equal percentage of reactions according to Cole(5), while arsphenamine is less apt to cause reactions as stated by Cannon(5). There must be factors of technique and classifications of reactions which will enter into and alter any figures on this subject. Scharnberg(31) feels that our guiding principle should be to employ remedies and methods which insure to the patient maximum curative effects against the disease with maximum security to the body tissues, and the second is the most important. He feels (Scharnberg) that neoarsphenamine is the safest drug to use.

The selection of the drug to be used or employed in the given case cannot be made except individually and should not be attempted. We do know that a patient sensitive to one arsenical drug(32) is apt to be sensitive to other arsenical drugs. This question of sensitiveness to drugs has been well covered, Shock (24) thinks
that in any patient who has a mild reaction, that a patch contact test should be done and if the result is positive, other drugs should then be searched for, if all the arsenicals cause a reaction in the test, arsenical therapy is not to be used. Sulzburger(26) however draws three interesting conclusions: 1-There exists in some individuals an apparently primary sensitization to arsenphenamine in contact tests. 2-Patients who have a positive test do not necessarily develop dermatoses upon the intravenous injection of the drug. 3-Patients with a negative contact test may develop dermatoses after injection. The intradermal sensitization of patients by accidents of injection is not a moot point and according to Sulzburger(33), is not as positive a factor as it was once thought to be.

One thing upon which there is agreement is the fact that a more careful check of patients during their courses of arsenical therapy would be advisable. Cole(34) would approve of a careful examination of the entire body and a complete urinalysis, combined with a careful questioning to elicit any complaints, before each injection. He states that many patients whom he has seen, have had another injection of arsenohenamine when they already had an arsenical eruption of the skin. Kile(18) has stated the contraindications to the use of arsenic as:

1-Well developed vascular abnormalities such as arteriosclerosis and severe cardiac lesions.
2-Severe parenchymatous involvement of important viscera.
3-Asthma or catarrhal infections of the upper respiratory tract.
4-Pulmonary tuberculosis.
5-Individual idiosyncrasy.

In regard to the prevention of arsenical reactions we could use certain rules:
1. Never give arsenic without careful questioning as to the last meal and last bowel movement.

2. Always be positive that there is no skin eruption present nor is there any pruritis.

3. Be sure that the patient is not anemic and that there is no history of hemorrhage, no matter how small.

4. Slow injection of dilute solutions and small dosage.

Other aids in the prevention of reactions are atropine, adrenalin, ephedrine, the divided technique of Bezredka, intravenous calcium gluconate, and the use of a glucose solution as a vehicle.

The treatment of arsenical reactions according to the literature at this time rests upon one thing, that is sodiumthiosulfate and in certain of the reactions, it is not indicated, it's use being fraught with some danger in some certain cases. Support and relaxation of the patient are things upon which all other treatment is based.

The early diagnosis of arsenical reaction is based on a careful cautious management of all syphilitic patients, together with the immediate recognition of any and all untoward signs or symptoms in a person undergoing treatment. The symptomatology is very diverse, in fact enough so, as to cover nearly anything, or everything, so that the diagnosis rests upon the elicitation of any symptom present early enough to ward off progression of the case to an obvious picture.
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