NEW DATA ON THE TREATMENT OF KALA - AZAR
(Mediterranean Visceral Leishmaniasis)

Paul Giraud, M.D.,* Rene Bernard, M.D., A. Orsini, M.D., and J. Coignet, M.D.

Kala - azar has always occupied an important place in the pathology of the Mediterranean region. Every year we observe the appeareance of a certain number of cases, most of which appear in children from the region of Provence. However, a certain proportion of these cases involve adults of all ages (up to 72 years). It is entirely possible that the emigration of large numbers of young city people to sub - standard regions of Algeria has given rise to numerous infections. This would seem to affirm the rural character of the disease.

The diagnosis of kala - azar is often difficult and it is not uncommon for the disease to run its course for a period of several months without being identified, proceeding through alternating periods of remission and relapse of increasing severity. Frequently the disease is diagnosed belatedly in regions where it is not endemic and where the practicing physicians do not normally expect to encounter it.

It is therefore prudent to consider the possibility of kala - azar in every case in which the patient presents the major symptoms of the disease : irregular fever, anemia and splenomegaly and, in addition, is known to have spent even a brief period in an endemic zone. We have noticed in recent publications accounts of late diagnosis or therapeutic errors which have sometimes resulted in the patient's death.

At the Medical Clinic for Children in Marseille, however, we have treated 360 cases of kala - azar since 1922. No deaths have been recorded since 1944 although we have had 123 cases under treatment during the ensuing 17 years. We feel that this sizable number of cases provides us with a substantial backlog of experience and information for handling the disease.

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* Professor, Clinique Médicale Infantile de Marseille, France.

In our cases recoveries occurred on an average of two to three months after treatment was instituted and recovery was usually without complication.

Thus kala - azar with proper diagnosis and treatment should become a disease that is curable within a reasonable period of time, such cures being complete and without relapse.

We are hopeful that in summarizing the results of our studies and in setting forth in detail the treatment we have developed others may be assisted in avoiding the errors we committed at the outset of our study.

We shall discuss first the stibiated products, which remain the basis of treatment, then the use of diamidines and, finally, supportive treatment.

1. Stibiated Products

Stibiated products were responsible for the first cures observed in a disease which, if left untreated, is always fatal. Here it is once again necessary to credit the school of Professor Jemmer, especially Drs. Christina and Caronia, who were the first to use this medication in 1915.

But antimony in therapeutic doses is relatively toxic and difficult to handle. The first medicinal forms (mineral or organic compounds) were found to be dangerous and capable of producing frequent serious, sometimes even fatal, accidents. We are also indebted to the doctors of this period for recording these accidents with accuracy and precision. At present we have available in France an organic product, antimony N methyl glucamine (Glucantime), which is very easy to manage and which gives us great efficacy combined with a large margin of security. Still it must not be forgotten that even with this product there is a possibility of incidents of intolerance or intoxication if one ignores the very precise rules governing administration of this medication.

Stibio - intolerance occurs primarily in the early days of treatment and is particularly frequent in cases where the disease has reached an advanced stage prior to the beginning of the treatment. The employment of large doses is conducive to the development of intolerance, but such can occur even with a relatively moderate dose and even after an initial seeming improvement.

The symptoms indicating intolerance are :

Hyperthermia. This is often violent, reaching or surpassing 40 C. and is frequently accompanied by a whooping type of cough and vomiting, indicating bulbar edema.

Various infections of an acute nature, often superimposed, making it difficult to distinguish between those attributable to intolerance of the medication and those arising from other causes. Such infections frequently attack the digestive tract, creating a picture of toxicity. This is particularly true in the case of infants. They can also assume the guise of dyspneic bronchopneumonia with infectious edema and a case of staphylococcia has been observed.

Hemorrhagic syndrome, very severe, which almost certainly results in death if intervention is not immediate and energetic.

We report in brief some case histories illustrating accidents of the sort described above. These have been culled from recent literature.

Case 1. Jambon and Bertrand.[1]

An adult of 42 years, who had contracted his infection in Gard, was put under treatment a year after the appearance of the first symptoms of the disease.

His hemogram at that point showed 2,600,000 red blood cells per cubic mm., 2,400 white cells per c. mm. and 46 per cent polymorphonuclear leukocytes. Obviously the disease was already in an advanced stage.

Treatment with Glucantime was immediately instituted with a dose of 10 cg./Kg. (7.5 Gm.) on April 20.

On April 23 diarrhea and increased salivation were noted. The dose was reduced to 6 Gm., but the medication continued.

On April 24 the patient's temperature rose to 40 C. and pleuropulmonary inflammation was present on the left side.

On April 26 mobilliform erythema appeared.

On April 29, with treatment still at 6 Gm./day the patient, after repeated convulsions, lapsed into coma.

On April 30 the patient expired.

Autopsy revealed cerebromeningeal edema with hepatization of both right and left lower lobes of the lung.

There is a question here of a mixed form of the disease in which intolerance of medication and infection were so closely associated as to make it difficult to determine their relative importance. It is significant that the dose of Glucantime was diminished, but not suppressed following the appearance of untoward symptoms.

Case 2. Chaptal, et al.[2]

An infant of 20 months was hospitalized on February 10, 1951, for a febrile splenic anemia which was diagnosed as kala-azar. After transfusions, treatment was begun with Glucantime administered in progressive doses: 5 cg./Kg., followed by 10 cg/Kg. every other day and then every day. After the eighth injection, despite temporary improvement in the patient's condition, hyperthermy developed with multiple localized staphylococcal lesions, laryngitis, purulent pleurisy and abscesses of hirsute areas. In spite of the fact that the stibiated treatment was discontinued and active antibiotic therapy instituted, death occurred following an encephalomeningeal episode.

In other cases, fortunately, the effect of intolerance has been less severe.

Doury[3] cites two cases of kala-azar contracted at Hoggar by children three and five years of age respectively. Between the eighth and tenth injections of Glucantime (at a dosage of 10 cg./Kg.) both children developed hyperthermy of 40 C. which persisted for several days and resisted antibiotic treatment. Fortunately cures were eventually brought about in both cases.

As examples of the hemorrhagic form of reaction we cite two cases drawn from the literature :

Case 3. Bernheim, et al.[1]

This was a child of 19 months who had developed serious kala-azar with accompanying anemia. His red blood cell count was 1,890,000 per c. mm. The disease was contracted at Ardeche and had persisted for several months.

Treatment was instituted on November 8, 1956, with 10 cg./Kg. of Glucantime each day without recourse to small initial doses.

On the fourth day there were numerous digestive hemorrhages (with hematemesis) which failed to respond to treatment with transfusions and Cortancyl. In view of the rapid deterioration of the patient and the high degree of thrombopenia, splenectomy was attemped. This intervention supported by transfusions of siliconized blood appeared to arrest the hemorrhagic condition.

Stibiated treatment, which had been withdrawn for two days, was resumed with small doses every other day at first and then daily. The treatment with cortisone was continued. Cure was finally established after treatment with Lomidine.

Case 4. Goudemand, Macquet, and Leduc.[5]

This was the case of an adult of 26 years who had contracted kala-azar in Algeria and whose condition had remained undiagnosed for many months. He was put on Glucantime at a dosage of 10 cg./Kg. After the 15th injection and after having shown marked improvement the patient expired as a result of uncontrollable digestive hemorrhages.

Autopsy revealed generalized purpura with no visible visceral lesions.

Because of such cases there has been an attempt to attribute these hemorrhagic accidents to the malady itself and to describe «The Hemorrhagic Forms of Kala - Azar». It is certain that the terminal stages of kala - azar as well as the more serious cases are frequently characterized by hemorrhagic syndromes of greater or lesser degree. This has always been known and so described. However, it is our opinion that antimony, particularly when given in large doses, encourages this tendency.

In these last two cases the doses were, according to our present standards, massive (10 cg./Kg.) and we ourselves had similar accidents during our first attempts at treatment with products which were less manageable than Glucantime.

On the other hand we can now report the complete elimination of such syndromes since we began to base our treatment on prudent progressive doses. Our last 123 cases bear witness to this.

In any case in which a patient, no matter what age, displays prior to treatment a tendency to hemorrhage, no matter how slight, it is necessary, we feel in the light of our experience, to begin treatment with either Lomidine or with guarded doses of antimony accompanied by transfusions.

The cases we have cited above prove that the age of the patient makes little difference. For example, two cases of adult kala - azar were reported in *Le Lille Medical* within a month of each other. One, which we cited above, was treated with 10 cg./Kg. of Glucantime and died of a hemorrhagic syndrome (March 1961) and the other was treated with a dose of 6 cg./Kg. and rapidly recovered (April 1961).

Stibio - intoxication can present the same clinical picture as intolerance and it is difficult in studying case histories alone, such as those we have just cited, to determine which is the case - intoxication or intolerance.

The debate is, however, without practical importance. One can perhaps more readily attribute accidents arising at the beginning of treatment to intolerance and those appearing at the end of the course to intoxication. In both instances one observes hyperthermia, acute infections and hemorrhagic syndromes. And in both cases it is necessary to stop treatment immediately, resuming again very slowly and with the utmost caution.

On the other hand there are some delayed reactions which can without doubt be attributed to intoxication. We now speak of the polyneuritic accidents.

Case 5. Portier, Boulard and Massonat.[6]

This was a patient of 21 years who had suffered from undiagnosed kala-azar for seven months and was found to have marked splenomegaly. Treatment with Glucantime was instituted with a dosage of 10 cg./Kg. (6 Gm.) daily for 15 days. Results were excellent in general.

However, during treatment, the lower limbs exhibited paresthetic symptoms. These developed into motor disturbances which hindered walking but gradually disappeared after a period of several months.

In the course of treating hepatic distomiasis with Glucantime, Brouet reports similar reactions, not severe, but necessitating the interruption of treatment; the reactions being persistent fever, erythema, joint pains and transitory renal attacks.

Stibio - Resistance has become rare owing to the tendency to employ large daily doses of Glucantime. Resistance develops when very low doses are employed or when treatment is interrupted too soon after the initial improvement. It is frequently observed in patients from uncooperative or uncomprehending families or from those familes who demand that a patient be returned home prematurely. Sooner or later, in cases such as these, one finds a recurrence of the disease and this recurrence is less receptive to stibio - therapy.

In cases of this type one is often inclined to advise the ablation of the hypertrophied spleen which appears to be an inaccessible refuge for parasites. Chaptal[7] has reported an example of this.

Case 6. (Personal)[8]. M. Jean, born March 2, 1957, entered the Children's Medical Clinic on June 13, 1959. He was a resident of Patrimonio, Corsica, and since birth had displayed psychomotor retardation, probably obstetrical in origin. The patient was hospitalized, not for this disorder, but for a febrile condition which had persisted for one and a half months.

Examination revealed an irregular fever and the liver palpable two fingers below the costal margin. The spleen was likewise clearly palpable.

Hemogram revealed a moderate anemia with leukopenia and granulopenia.

Myelogram was within normal limits and no parasites were found in the feces. Ganglionic biopsy and histological examination, however, revealed the presence of numerous Leishmania.

Treatment with Glucantime was instituted with the administration of progressively increasing doses eventually attaining the level of 6 cg./Kg. with daily injections for a period of 15 days. Treatment was well tolerated. The fever subsided and the spleen decreased in size.

Treatment with Lomidine was then begun promptly, 15 injections, three a week, with doses increasing from one - half to two cc. The patient remained

afebrile, the liver was normal as was the hemogram and only the spleen remained slightly palpable. The patient's family was anxious to return to the native village, and on August 10, 1959, the patient was removed from the hospital. The fact that it was vacation time was instrumental in our acquiescence to the patient's release at an obviously premature date.

The child remained in good condition throughout the winter. However, his spleen continued palpable. Attention was then directed towards his psychomotor retardation.

He was readmitted to the clinic on June 14, 1960 with a recurrence of fever of one month's duration.

His liver had again increased in size and his spleen was extremely large, reaching to the left iliac creast - far greater than it had been at the time of his previous admittance. The hemogram presented the same picture as before: anemia, leukopenia and granulopenia. Protein determination studies revealed a reappearance of «clocher» of gamma globulin, but it was not possible to uncover evidence of Leishmania by myelogram.

Treatment with Glucantime was reinstituted on June 15 with a dose of 6 cg./Kg. with daily injections for a period of 15 days. This was followed by a course of Lomidince, 14 injections of 2 cc. each, three injections each week.

During this course of treatment with diamidines, oliguria and slight albuminuria were noted. Azotemia elevated to 2 Gm. and then to 3 Gm. without corresponding clinical signs.

These biological signs of renal attack gradually disappeared in a period of approximately three weeks.

A second course of treatment with Glucantime had been scheduled to fortify the initial course. However, the plan was abandoned after only three injections.

The hemogram returned to normal.

The liver rapidly resumed normal size, but the spleen remained slightly palpable below the left costal margin.

The patient seemed to have been cured of his kala - azar and there was no remission as of the date of his last examination in June 1961 although the spleen continued to be very slightly palpable.

This case presents a good illustration of stibio - resistance after what would normally be considered under - treatment.

In this case it was not possible to find Leishmania at the time of relapse and the treatment course presented more difficulties and proved less efficacious than it had previously.

We point out that in our case relapse came one year after the initial attack. We should also like to draw attention to the severe renal attacks observed during the course of treatment with Lomidine. We shall return to this point later.

2. The Diamidines

Diamidines are drugs which in themselves can achieve recovery in certain cases of kala - azar.

Like others before us, we have had total and definitive cures through utilizing these drugs. But recovery is slower and less certain if one employs them exclusively.

In practice we use Pentomiodine (Lomidine) in doses ranging from one - half to four cc., according to the age and weight. That is to say, 20 to 160 mg. (roughly two to two and one - half mg./Kg.) in intramuscular injections every second day. We start with half of the dose for the first three injections and then increase to the full dose for the next 12 injections (15 in all).

We have for some time considered this drug to be harmless, even when administered in large doses. However, recent experience leads us to believe that, as in the case of antimony, one must proceed with caution.

There is first a local discomfort, pain at the point of injection, accompanied by swelling of the buttock and minimal local bleeding. These symptoms do not cause great concern in a hospital where there is a tendency to minimize the «caprice de l'enfant.» However, within many families they assume great proportions. Thus, we have abandoned this drug as a means of external treatment.

There are signs of intolerance which are more often than not transient in nature, but which can become acute on occasion.

We have mentioned the renal attack with accompanying albuminuria and the elevation of azotemia up to three Gm. (Case 4) resulting from the withdrawal of the medication without special therapeutics.

Also we have called attention to hyperglycemia with or without glycosuria and hypothermy. A periodic urine analysis is therefore obligatory, at least during the period of treatment. In Doury's article cited above[3] one finds the following observation :

Case 7.

A two and one - half year old child from a family of low income and education level, suffered from kala - azar of many months duration. Since the parents refused to consent to more than a short period of hospitalization, very rapid treatment with Lomidine was instituted, employing relatively high doses of 2 mg./Kg. for the first two days followed by 4 mg/Kg. for the ensuing ten days (one injection daily).

The initial injections induced apyrexia and the spleen decreased in size. On the eighth day hypothermia was noted at 35 C. and the pulse rate dropped to 55/min. On the basis of the reputed innocuous character of the drug being administered, the patient was continued on high doses. Presently the patient emitted black vomitus, adynamia became apparent, the pulse accelerated and was difficult to detect. Death was attributed to syncope.

The authors feel that this death was the direct result of Lomidine intoxication. In fact, in our treatment of canine leishmaniasis with Lomidine we have attempted to greatly increase the doses administered only to have the animals expire. We did not believe at the time, however, that clinical application with human patients would produce similar results.

Consequently, it is important to remember that while diamidines are as a general rule well supported by the patient, doses must be controlled and treatment guarded. Regular clinical examinations, including urine analysis, are essential for the detection of early signs of drug intolerance.

3. Transfusions

Transfusions, administered with the usual care and precaution, are beneficial and do not aggravate the condition.

The more severe the case, the more marked the initial anemia and the more effective is the transfusion given with particular regard to the appearance of a benign hemorrhagic incident. Such transfusions can be repeated advantageously during treatment, particularly in cases that indicate a drug intolerance. Transfusions, however, do not have any direct effect on the course of the disease and can only be regarded as supportive measures.

4. Antibiotics

Likewise antibiotics cannot produce a cure. This fact was established when these drugs were employed prior to diagnosis as treatment for a febrile condition of uncertain origin. They were ineffective.

5. Anti - Inflammatories

We have elsewhere mentioned the use of the anti - histamines in cases of intolerance, but we must emphasize that subsequent use of these drugs has failed to produce unqualified results and we no longer use them.

Techniques of Treatment

It is our recommendation that the treatment of leishmaniasis in all age groups be as follows :

Stibiated treatment should be instituted immediately with Glucantime, 15 intramuscular injections per day, the first three injections to be guarded doses of one - fourth to one - half centigrams per kilogram, the other twelve injections to be six centigrams per kilogram.

This dosage should *never* be increased for such would result in a severe accident for the patient, possibly even death.

In all cases, particularly those of more serious nature, transfusions should be instituted at an early date. The primary stages of the disease as well as the period prior to termination of the malady are the most important and potentially dangerous phases. In the event of any sign of intolerance (hyperthermy, acute infection, hemorrhage) stibiated treatment should be stopped immediately and repeated transfusions given. After a sufficient period of waiting, treatment can be reinstituted with the patient on very small doses. As an alternative the patient can be put on diamidines.

Stibiated treatment should be followed immediately by treatment with diamidines. Fifteen injections must be given within a 48 hour period, the first three doses being guarded, the last 12 being from 2 miligrams to 2.5 miligrams per kilogram of weight. It is imperative to examine the urine for sugar, albumin and eventually for azotemia during the initial period of treatment when the drugs are difficult to tolerate.

After the treatment with diamidines, it is necessary to revaluate the disease. Clinical examination with particular attention to the liver and spleen, biologic examinations (hemogram, serum proteins and, in due course, a repeated search for Leishmania) are essential. If the clinical and biological status of the patient seem normal and the spleen is not palpable, the patient can be put on an outpatient basis with continued observation for some months in order to be assured of complete recovery.

Should a symptom persist, giving rise to concern (especially anemia or an enlarged spleen), a second course of stibiated treatment should be started, using the same doses as previously tolerated. This has always achieved a complete and definitive recovery.

We should like to emphasize that the treatment prescribed above can only be successfully concluded when the patient is hospitalized.

Based upon the experience of 17 years in which time this technique was applied to 123 patients, we wish to repeat that recovery can be obtained by the above method in a period that does not exceed two to three months in the majority of cases.

Summary

The authors wish to call attention to the fact that in recent medical publications severe and many times fatal accidents during treatment of visceral leishmaniasis in both children and adults are reported.

They emphasize the fact that their opinion is based upon their experience since 1922 when they first started their study of the disease and their actual clinical experience since 1944 when they began their work with the actual techniques of treatment. They feel that kala - azar is a disease that can be cured in a period of two to three months with proper treatment.

To prevent severe complications, the utmost caution must be used in the administration of treatment.

Kala - azar, a disease which undetected and untreated causes almost certain death, can, in the present day, be cured within a reasonable period of time.

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