BAL IN THE TREATMENT OF GOLD TOXICITY

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Gold is generally regarded as a useful therapeutic agent in the treatment of rheumatoid arthritis. Unfortunately its administration, however carefully supervised, is attended by the risk of various toxic reactions, some of which may be fatal. Until the introduction of BAL, no specific treatment was available for such toxic reactions. Favourable results with this drug have lately been reported from America in twenty cases described by various authors, and in three cases in this country.

Research carried out by Peters and his colleagues (1945) led to the discovery of BAL, and to its use as a therapeutic agent in the treatment of toxic reactions to heavy metals. Further experimental work carried out in America confirmed and elaborated the findings of these workers (Waters and Stock, 1945). Essentially, BAL acts by competing with tissue cells for certain metals. It forms with the metal a stable compound which is as a rule non-toxic and which is believed to be rapidly excreted. BAL proved highly successful in the prevention and treatment of lewisite burns (Stocken and Thompson, 1941; Vey, 1941); in the treatment of the complications of arseno-therapy (Carleton and others, 1946; Longcope and others, 1946); and in the treatment of acute mercury poisoning (Longcope and Luetscher, 1946). The experimental work of Long and Farah (1946) suggests that it may be of use in severe reactions due to mercurial diuretics. BAL may also be found to be effective in poisoning due to the inhalation of zinc fumes (Annotation, *Nature*, 1946), and may have an application in veterinary medicine in diseases of copper metabolism in sheep (McDonald, 1946).

Among the first papers on the use of BAL in toxic reactions due to gold was that of Ragan and Boots (1947). Before using the drug in human subjects suffering from gold toxicity these authors carried out an important preliminary experiment. While BAL combines with heavy metals to form a compound that as a rule is non-toxic, that compound formed with cadmium causes acute nephritis. Ragan and Boots demonstrated that animals

treated simultaneously with gold and BAL showed no toxic effects in heart, liver, or kidney. BAL was then used in five cases of rheumatoid arthritis with gold dermatitis in man, with a good result in four instances. In all cases a significant increase in the urinary excretion of gold occurred coincident with the administration of BAL. Four patients had an exacerbation in symptoms due to rheumatoid arthritis within one month of this treatment. Cohen and others (1947) reported five cases, three with gold dermatitis, one with pruritus and conjunctivitis, and one with stomatitis, treated successfully with BAL. Margolis and Caplan (1947) found BAL of benefit in one case of severe stomatitis and in one case of mild conjunctivitis, anal ulceration, and dermatitis; they claimed amelioration of long-standing exfoliative dermatitis in two cases; in one case of mild dermatitis no appreciable benefit was obtained. Margolis and Caplan concluded that the early use of BAL in the treatment of toxic effects resulting from the administration of gold appeared to be of value. Davison (1947) successfully treated three early cases of gold dermatitis. Lockie and others (1947) obtained a spectacular recovery in two serious reactions to gold; one reaction was thrombocytopenic purpura, and the other agranulocytosis. In this country three cases of gold dermatitis have been treated successfully with BAL (Slot and McDonald, 1947; Simpson, 1948).

In the present paper the results of the use of BAL in fifteen cases of gold toxicity are described; the series includes two cases of acute hepatitis due to gold, in which condition its use has not hitherto been reported.

Clinical Findings in the Present Series

The fifteen cases in the present series consist of eleven patients with dermatitis; two of these had stomatitis in addition. In one case stomatitis was the only toxic reaction. Two patients had acute hepatitis and one had hypoplastic anaemia.

A summary of each case is given in the Table. In addition four sample cases are described more fully to expand and illustrate the Table. One case of dermatitis, one of dermatitis and stomatitis, and two of hepatitis have been chosen for this purpose. It was felt that a fuller description of the two patients suffering from hepatitis would be of special interest as toxic reactions of this type have not previously been described treated with BAL.

Case Records

Case 1.—A married woman, aged 39 years and weighing 70 kg., who had suffered from rheumatoid arthritis since November, 1946, received 0.58 g. of myochryesine. The last five doses were of 0.1 g., and the final dose was given on June 11, 1947. Dermatitis developed on June 18, and by June 30 was of a generalized exfoliative nature and still spreading. On that day treatment with BAL was commenced in successive daily doses of 400 mg., 200 mg., 200 mg., 200 mg., 100 mg., and 100 mg. intramuscularly. Individual doses were of 100 mg. There were no toxic reactions, and forty-eight hours after the commencement of treatment improvement was present, best seen in diminished swelling of the face. There was also a marked decrease in pruritus. Steady improvement continued until July 21, when the only finding was a few non-irritant papules on the legs. A slight exacerbation in the following week subsided spontaneously. On Sept. 13 a scaly eruption the size of a halfpenny was present on the dorsum of the left foot, and this had disappeared by Nov. 15. When the patient was last seen on the latter date there had been no recurrence of arthritic symptoms.

Case 10.—An unmarried woman, aged 24 years and weighing 63 kg., who had had rheumatoid arthritis for eighteen months, was treated with 0.68 g. of myochryesine. The last six doses were of 0.1 g. and the last injection was given on July 20, 1947. On July 6, 1947, a sore mouth developed, followed by ulcers of the tongue and gums and on July 20 by an itching rash on the hands. The patient was admitted to hospital on July 21 with severe stomatitis and moderate dermatitis of the hands. On July 23 dermatitis was present on the anterior aspect of both legs.

On July 25 both conditions were deteriorating, and on successive days BAL was given intramuscularly in doses of 400 mg., 200 mg., 200 mg., 200 mg., 100 mg., and 100 mg. Transient local pain and nausea followed the earlier injections of BAL, but twenty-four hours after the first injection the patient announced she was "better", and forty-eight hours afterwards reported that the soreness of the mouth was less and that the itch had gone. By July 28 the dermatitis was less extensive and less erythematous, and the ulcers of the mouth were healing. When the patient was discharged on Aug. 3 the stomatitis was healed and some desquamation of the right palm was the only residual evidence of dermatitis. On Aug. 16 this was still evident, and one small ulcer was present in the mouth. On Oct. 11 there was no dermatitis or stomatitis and no residual pigmentation. On

Nov. 15 there was no evidence of any relapse in the rheumatoid arthritis.

Case 13.—A married woman, aged 51 years and weighing 47 kg., had suffered from rheumatic mitral stenosis, auricular fibrillation, and intermittent attacks of congestive heart failure for three years; rheumatoid arthritis had been present for about the same length of time; symptoms from the arthritis were severe and treatment with myochryesine was begun on Oct. 14, 1947. By 12 Dec. 0.38 g. had been given, with an improvement in the arthritis; the largest dose administered was 0.05 g. On Dec. 17 the patient complained of having felt profoundly exhausted for two or three days. She gave the appearance of being a seriously ill woman. A slight icteric tinge was present and the urine contained urobilinogen in excess. The liver was not enlarged. The icteric index was 17 units (Meulengracht). Old hepatitis was diagnosed, and on Dec. 18 treatment with BAL was begun in successive daily doses of 200 mg., 300 mg., 300 mg., 300 mg., and 200 mg. There were no local reactions, but immediately after the last injection the patient complained of nausea, epigastric discomfort, and some diarrhoea. BAL was stopped, and symptoms subsided within twenty-four hours.

Within forty-eight hours of the first injection there was marked subjective and objective improvement. Tiredness was less, and the icteric tinge disappeared. Urobilinogen was present in the urine in excess until Dec. 21, that is, four days after the commencement of BAL. On and after that date urobilinogen could no longer be demonstrated. The icteric index was unfortunately not repeated until Jan. 5, 1948, when the reading was 8 units. At this time the serum albumin was 3 g. per cent. and the serum globulin 2.8 g. per cent.

The patient remained well until Jan. 19, when tiredness and drowsiness returned. Her temperature rose to 102° F., and she complained of frequency of micturition and dysuria. The urine contained numerous pus cells, and a profuse growth of *B. coli* was obtained on culture. The icteric index was 9 units. Treatment with sulphanimide, 1 g. thrice daily, was begun. On Jan. 21 the urine contained urobilinogen in excess and the icteric index was 15 units. Next day 300 mg. of BAL, and on 23 Jan. 200 mg. were injected in doses of 100 mg. Severe abdominal pain, intense nausea, and repeated vomiting followed the injections of BAL, which had to be stopped with resultant improvement in the abdominal symptoms by the following day—Jan. 24. On this date the urine contained no pus but urobilinogen in excess. Though the vomiting had ceased the patient's general condition was still very poor. She was tired, drowsy, and had a yellowish, muddy complexion. The liver was two finger-breadths enlarged; the icteric index was 34 units. On Jan. 27 drowsiness was extreme, the patient was irresponsive, and at noon the prognosis appeared hopeless. BAL, 100 mg., was injected at 3 p.m. and 4 p.m. Following the second dose there was improvement; she was less drowsy, replied to questions, and admitted an improvement. This continued slowly over the next few days: 100 mg. BAL was given on Jan. 28 and 30, and from Feb. 2 to 7 inclusive. On Feb. 4 the icteric index was 22 units. By Feb. 6 there

TABLE
DETAILS OF FIFTEEN CASES OF GOLD TOXICITY TREATED WITH BAL

Case	Age yrs.	Wt. kg.	Diagnosis	Total dose gold (g.)	Toxic effects	Delay in therapy	Dose of BAL (mg.)	Toxic effects of BAL	Result	Follow-up	Relapse in R.A.
1	39	70	R.A.	0.58	Exfoliative dermatitis	12 D	1,200 in 6 D	0	Decrease in pruritus within 48 hours. Progressive regression in dermatitis. No further lesions. Only minimal residual in 3 W. No residual pigmentation.	5 M	0
2	53	60	R.A.	0.38	Dermatitis (general- ized)	4 W	1,200 in 6 D	0	Pruritus less in 2 D and almost nil in 4. Dermatitis much less erythematous and less extensive in 6 D; more scaly. No more lesions. Hyperkeratosis of skin persisted for about 3 M. No residual pigmentation.	5 M	0
3	49	68	Osteo- arthritis	0.88	Dermatitis (general- ized)	3 M	1,200 in 4 D	0	Slight improvement within 1 W, by which time rash had changed in character all areas, now marked follicular hyperkeratosis. Hair ceased coming out. Skin quiescent 6 W later. No further lesions. Pigmentation minimal.	6 W	N.A.
4	39	70	R.A.	0.75	Dermatitis (general- ized)	1 M	1,200 in 6 D	Anorexia for 1 W. Urticaria at site of infect. 19 D after BAL. Con- trolled by Benadryl	Two W later no itch, less erythema, plaques smaller. No further lesions. When seen after 2 M, skin virtually healed.	2 M	Return of joint pains

R.A. = Rheumatoid Arthritis; M = month; W = week; D = day.

TABLE (continued)

Case	Age yrs.	Wt. kg.	Diagnosis	Total dose gold (g.)	Toxic effects	Delay in therapy	Dose of BAL (mg.)	Toxic effects of BAL	Result	Follow-up	Relapse in R.A.
5	29	60	R.A.	0.58	Dermatitis (general- ized)	2 M	1,200 in 3 D		Free from pruritus in 3 D. Steady decrease in extent of dermatitis. No further lesions. Change to appearance of follicular hyper- keratosis within 10 D. For 1 M some dermatitis still pre- sent but still decreasing and appeared quiescent.	1 M	0
6	50	77	R.A.	1	Pruritus (severe)	2 W	100 in 1 D as O.P.	0	One W later reported marked and maintained decrease in itch.	7 M	0
7	63	65	R.A. Benign hyperten- sion	0.75	Dermatitis limbs (mild)	4 M	200 in 1 in- ject. as O.P.	0	Two W later severe pruritus had disappeared. Dermatitis less extensive and more quies- cent.	0	
8	47	77	R.A.	1	Dermatitis buttocks (mild)	8 W	300 in 1 in- ject. as O.P.	Numbness of legs for 2 D. Las- situde for 4 D	Pruritus absent in 4 D. Derma- titis less extensive, less erythe- matous and more scaly in 1 W.	0	
9*	57	75	R.A.	0.93	Dermatitis limbs (mild)	4 M	300 in 1 in- ject. as O.P.	0	Two W later doctor reported: "No further spread and no new lesions. Apparent healing. No itch."	0	
10	24	63	R.A.	0.68	Dermatitis limbs; stomatitis severe	19 D	1,200 in 6 D	Minimal local pain and nausea	Disappearance of pruritus in 2 D. Dermatitis less extensive and less erythematous in 3 D. No further lesions. Desquamation of palms only in 9 D. Skin healed in 2-3 M. No residual pigmentation. Stomatitis healed in 9 D.	4 M	0
11	59	44	R.A.	0.47	Dermatitis (general- ized); stomatitis slight	1 W 2 M	1,200 in 3 D	Local pain and nausea after initial injection only	Dermatitis. Decrease of pruri- tus and apparent regression of dermatitis in 3 D. Relapse 4 D later controlled by 150 mg., 200 mg., and 150 mg. BAL at weekly intervals as O.P. Stom- atitis. Improvement in 3 D. Minor relapse healed rapidly.	1 M	0

R.A. Rheumatoid Arthritis; M=month; W=week; D=day.

TABLE (continued)

Case	Age yrs.	Wt. kg.	Diagnosis	Total dose gold (g.)	Toxic effects	Delay in therapy	Dose of BAL (mg.)	Toxic effects of BAL	Result	Follow-up	Relapse in R.A.
12†	47	60	R.A.	0.68	Stomatitis	0	1,200 in 6 D	0	No further lesions after 24 hours. Less pain in 2 D. Progressive healing, complete in 1 W.	0	
13	51	47	R.A. Mitral stenosis Pyelo- nephritis	0.38	Hepatitis	5 D	1,300 in 5 D	Nausea, epigastric pain, and diarrhoea subsiding on stop- ping BAL	Marked improvement in 48 hours. Urobilinogen disappeared from urine in 4 D. Icteric Index fell from 17 to 8 units.	4 M	0
					Relapse of hepatitis 1 M later	0	500 in 2 D	Nausea, vomiting and severe abdominal pain	No improvement.		
					Later, when apparently improved, 1,000 mg. in 11 D		4 D	0	Immediate dramatic improve- ment. Urobilinogen disap- peared from urine in 8 D. Icteric index fell from 34 to 13 units in 14 D.	2 M	0
14	60	59	R.A.	0.6 g. in 3 doses	Hepatitis	10 D	1,000 in 4 D 1 W later 1,200 in 4 D	Minor local pain only 0	Immediate improvement in ano- rexia and lassitude. Urobili- nogen in urine decreased to nil in 2 W. Icteric index fell from 18 to 8 units in 10 D.	1 M	0
15	34	58	R.A. Bronchiec- tasis	6 courses: last 0.08 g. only	Hypoplastic anaemia	10 M	750 in 4 D	Pyrexia might be due to bronchi- ectasis	No significant change in peri- pheral blood or bone marrow before or after BAL.	3 M	0

R.A. = Rheumatoid Arthritis; M = month; W = week; D = day.

† This patient was first seen in the healing stage.

was no excess urobilinogen in the urine, and this finding persisted. By this time the patient's general condition was very much improved. On Feb. 9, 1948, the icteric index was 13 units, the gold sol test positive (2), and plasma proteins were albumin 2.6 g. per cent. and globulin 2.9 g. per cent. On March 1 the patient was allowed up, and by March 27 had shown no relapse in the rheumatoid arthritis. The joints, indeed, continued to show a steady improvement.

Case 14.—A married woman, aged 60 years and weighing 59 kg., had suffered from rheumatoid arthritis for two years. A course of myochrysine was begun on Jan. 2, 1948. As a result of a dispenser's error she had on successive weeks 0.1 g., 0.2 g., and 0.3 g., the last being given on Jan. 16. When seen on Jan. 24 she complained of severe nausea, anorexia, and extreme exhaustion. The liver was not enlarged but the icteric index was 18 units and the urine contained urobilinogen in excess. BAL was begun on that day, and on successive days 200 mg., 300 mg., 300 mg., and 200 mg. were given in doses of 100 mg. The patient's symptoms showed prompt improvement and the quantity of urobilinogen in the urine decreased. The icteric index on Jan. 28 was 12 units. On Jan. 30 it was 9 units, and the cephalin flocculation test was positive. As she continued to show a small excess of urobilinogen in the urine, and in view of the relapse that had occurred in Case 13, a second course of BAL, 300 mg. daily, was given from Feb. 3 to 6 inclusive. On Feb. 3 the icteric index was 8 units, and by Feb. 7 the urine contained no urobilinogen. The patient had no complaints. The symptoms due to the arthritis had disappeared, and when she was seen again on Feb. 8 there had been no relapse either in the arthritis or the hepatitis. The icteric index on that date was 10 units, the cephalin flocculation test negative, the serum albumin 4.66 g. per cent., and the serum globulin 2 g. per cent.

Discussion

Dermatitis.—From the results obtained in the eleven cases of gold dermatitis it may be concluded that BAL probably influenced favourably the course of gold dermatitis. A constant finding was the immediate decrease in pruritus. In many cases this disappeared within a few days of commencing the drug. It is more difficult to assess the effect of BAL on the actual eruption. In only one case was the eruption severe. In many of the cases it was mild, and might have been expected to have cleared up spontaneously in a matter of two or three months at the most. On the other hand, although there was no uniform immediate dramatic change in the course of the dermatitis, a steady improvement was evident in all cases in the weeks following the administration of BAL. In only one case did fresh lesions appear after the drug had been prescribed. Further studies in conjunction with the Department of Dermatology are in progress in an attempt to assess the effect of BAL on the course of the dermatitis. It is noteworthy that in the present series

improvement in pruritus and in the course of the eruption was not confined to early cases.

Stomatitis.—The three cases of ulcerative stomatitis, one of which was very mild, rapidly healed while under treatment with BAL. In the severer cases there was an immediate and striking improvement in local pain.

Hepatitis.—In acute hepatitis a gratifying response was obtained in the two cases treated. In the case which relapsed it may fairly be claimed that BAL proved life-saving. The toxic reactions due to BAL that occur in cases of hepatitis are discussed later.

Hypoplastic Anaemia.—No improvement was obtained in one case of hypoplastic anaemia due to gold. The interval between the course of gold and the administration of BAL was ten months. It is known that gold may continue to be excreted in the urine for many months after its administration (Freyberg and others, 1941). It was for this reason that BAL was tried, on the assumption that the minute quantity of gold still presumably present might be enough to depress the bone marrow, and its removal by BAL might result in improvement. No change in the peripheral blood or bone marrow was evident after the administration of BAL. Presumably gold had caused irreversible changes in the marrow.

Toxic Reactions to BAL.—The dosage initially used was that recommended by Peters and his colleagues (1947) for adults of average weight, 400 mg. on the first day, 200 mg. on the second, third, and fourth days, and 100 mg. on the fifth and sixth days. Few toxic reactions were encountered in the present series with this dosage, and as experience was gained the dose was increased. Experimental work, mainly on human volunteers, has been carried out by Sulzberger and others (1946), and by Modell and others (1946). These authors showed that up to 5 mg. BAL per kilo of body weight can be given with minimal or no toxic effects, and that in doses up to 8 mg. per kilo the effects are transitory. Toxic effects produced by this dosage usually begin about twenty minutes after the injection, with a return to normal in from forty-five minutes to two hours. Among the toxic effects produced are various paraesthesiae, lacrimation, blepharo-spasm, nausea, abdominal pain, vomiting, unrest, exhaustion, and a transient rise in blood pressure. Local pain at the site of the injection is frequently encountered. Though sensitization of the skin is common in cases where BAL is applied locally, sensitivity reactions in the skin have not followed intramuscular injections. Sulzberger and others (1946) produced skin sensitization as demonstrated by positive patch tests in five of

eighteen subjects. In four of these patients later intramuscular injection of BAL did not produce any cutaneous reactions. Abscesses at the site of injection have been reported by Cohen and others (1947) in cases of dermatitis.

In the present series single doses of up to 4 mg. per kilo body weight have been given with only transient discomfort, mainly in the form of pain at the site of injection. With subsequent injections this often became less marked. In no case did an abscess develop. In one case (No. 4) skin sensitivity developed at the site of injection but this was readily controlled by benadryl.

In one of the cases of hepatitis severe toxic reactions followed the administration of BAL. This is in keeping with the conclusions of Cameron and others (1947). These authors produced renal or hepatic damage in experimental animals, and then administered BAL. They found that full doses of the drug could be given safely in the presence of severe kidney damage, but that in the presence of impaired liver function BAL must be given cautiously, as toxic reactions of variable severity, and even fatalities, resulted from doses well below the fatal level for normal animals. In cases of gold hepatitis it is almost certainly unwise in single doses to exceed 3 mg. of BAL per kilo of body weight, and sometimes even smaller doses may be necessary.

It may be concluded, therefore, that in cases of gold toxicity, other than hepatitis, BAL may be administered in single doses of up to 4 mg. per kilo of body weight with minimal toxic reactions, and that such as occur will subside rapidly within one or at the most two hours. Such single large doses of BAL may therefore be given to out patients with equanimity provided the patient is kept under observation for about one hour after the injection. BAL used in this way may have a useful clinical application which will be discussed later.

Relapse in Rheumatoid Arthritis.—It has already been noted that Ragan and Boots (1947) found that four of their five cases showed an increase in the symptoms of rheumatoid arthritis within one month of treatment with BAL. In the present series six cases have been followed up for periods of one to six months and only one of these showed any relapse. This patient had previously relapsed following a course of gold without BAL.

Excretion of Gold.—The urinary excretion of gold was estimated by Dr. Crawford in the Department of Pharmacology, in three of the above cases using the method of Block and Buchanan (1940). This was the method used by Ragan and Boots (1947), when they showed an increase in the urinary excretion of gold coincident with the administration

of BAL. In the three cases of the present series where this was estimated there was no such definite increase. It was noted, however, that the results by this method proved unsatisfactory as judged by the estimation of duplicate samples. We have, therefore, no further evidence as to whether the excretion of gold in the urine is or is not increased. The test is difficult and time-consuming, and it is felt that the inaccurate results obtained in our hands are worth noting.

Dosage of BAL.—Though relapse in the symptoms of rheumatoid arthritis following treatment with BAL has not been a feature of the present cases, it is probably undesirable for several reasons to use BAL in quantities larger than necessary to control the toxic symptoms. In the first place, though BAL has not resulted in an increase in the symptoms of rheumatoid arthritis in the present series, the experience of others has led to a different conclusion, and a larger series of cases may prove relapse in the rheumatoid arthritis to be a frequent undesirable sequel to BAL therapy. On theoretical grounds relapse would be expected if BAL resulted in an increase in urinary excretion of gold. Secondly, it is well known that cases of rheumatoid arthritis developing toxicity often show a very good improvement in the joint symptoms. Over-treatment of the toxic reactions may therefore be undesirable. Lastly, gold toxicity is usually insidious in its onset; the risk is that it may progress to a dangerous degree, for example, from mild dermatitis to severe exfoliation, or from mild hepatitis to acute yellow atrophy. If the toxic reaction can be controlled at an early stage such danger may be averted and the beneficial effect of gold on the joints be allowed to continue.

It has been shown that BAL may safely be administered to out patients. It is suggested, therefore, on the first sign of gold toxicity, other than hepatitis, and persisting in spite of stopping gold, that BAL may be given in a single intramuscular injection of up to 4 mg. per kilo of body weight in the hope that this will control the toxicity without unduly interfering with the therapeutic effect of the metal. The case can be reviewed from week to week or at shorter intervals, and further single injections of BAL may be given if necessary. BAL has been used in this way effectively in four cases in the present series (Nos. 6 to 9), and further trials are being continued along the same lines.

Where severe toxicity is present, such as exfoliative dermatitis, ulcerative stomatitis, and probably nephritis, agranulocytosis, and thrombocytopenic purpura, more energetic treatment will be required. Work by Wexler and others (1946) on arsenic

poisoning suggested that four-hourly dosage would result in a maintained excretion of that metal. If there is any parallel in gold toxicity, a similar interval between doses is possibly indicated. Such an interval between injections would allow ample time for any reaction to subside and be assessed before the treatment is continued. Sulzberger and others (1946) have shown that no cumulative effects occur in doses up to 5 mg. per kilo at four-hourly intervals. In the cases instanced above, BAL could probably be administered with advantage in quantities up to 4 mg. per kilo of body weight at four-hourly intervals, omitting the night dose, for two or three days according to the improvement obtained. Amounts as large as these have not been repeated at such short intervals in the present series, but trials with this dosage are in progress. It is suggested that 3 mg. per kilo at six-hourly intervals for three or four days would be an adequate and safe dose for cases demanding energetic treatment, such as those under discussion. The work of Sulzberger and others (1946) suggests that, if necessary, a second course of BAL can be given without danger of sensitivity. No ill effects were noted in the present series in the three cases in which additional doses or courses of BAL were administered (Nos. 11, 13, and 14). Weatherall (1948) has pointed out that prolonged treatment with BAL may be dangerous. Cats treated in this way developed anorexia, loss of weight, and a rise in the non-protein nitrogen of the blood (Modell and others, 1946). In the short courses recommended such reactions are unlikely, and they were not encountered in this series.

Summary and Conclusions

Previous work on BAL with particular reference to its use in patients suffering from toxic reactions to gold is reviewed. The use of BAL in fifteen such cases is described.

BAL appears to be of value in the treatment of gold toxicity. In dermatitis the immediate improvement in the pruritus is a constant and striking feature, and the course of the eruption is probably influenced in a favourable manner. BAL is also effective in the treatment of stomatitis and hepatitis due to gold.

Toxic effects are minimal in doses up to four milligrammes per kilogramme of body weight, except in cases of hepatitis—in which it is confirmed that BAL must be given in smaller doses if severe reactions are to be avoided.

Relapse of symptoms due to rheumatoid arthritis following the administration of BAL was not a feature of the present series.

No conclusion could be made about the excretion of gold in the urine following BAL therapy.

Recommendations are made about the dosage, partly from a consideration of the previous literature on the subject, and partly from the limited experience obtained in the present series of cases. A distinction is drawn between the use of the drug in the treatment of mild and severe toxic reactions.

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REFERENCES

- Annotation (1946). *Nature*, **157**, 218.
 Block, W. D., and Buchanan, O. H. (1940). *J. Biol. Chem.*, **136**, 379.
 Cameron, G. R., Burgess, F., and Trenwith, V. S. (1947). *Brit. J. Pharm.*, **2**, 59.
 Carleton, A. B., Peters, R. A., Stocken, L. A., Thompson, R. H. S., and Williams, D. I. (1946). *J. clin. Invest.*, **25**, 497.
 Cohen, A., Goldman, J., and Dubbs, A. W. (1947). *J. Amer. med. Ass.*, **133**, 749.
 Davison, R. (1947). *Stanford Med. Bull.*, **5**, 37.
 Freyberg, R. H., Block, W. D., and Levey, S. (1941). *J. clin. Invest.*, **20**, 401.
 Lockie, L. M., Norcross, B. M., and George, C. W. (1947). *J. Amer. med. Ass.*, **133**, 754.
 Longcope, W. T. and Luetscher, J. A. (1946). *J. clin. Invest.*, **25**, 557.
 —, —, Wintrobe, M. M., and Jager, V. (1946). *Ibid.*, **25**, 528.
 Long, W. K., and Farah, A. (1946). *Science*, **104**, 220.
 McDonald, I. W. (1946). *Nature*, **157**, 837.
 Margolis, H. M., and Caplan, P. S. (1947). *Ann. int. Med.*, **27**, 353.
 Modell, W., Chenoweth, M. B., and Krop, S. (1946). *J. Pharmacol.*, **87**, Suppl. 33.
 —, Gold, H., and Cattell, M. (1946). *J. clin. Invest.*, **25**, 480.
 Peters, R. A., Stocken, L. A., and Thompson, R. H. S. (1945). *Nature*, **156**, 616.
 —, and others (1947). *Lancet*, **2**, 497.
 Ragan, C., and Boots, R. H. (1947). *J. Amer. Med. Ass.*, **133**, 752.
 Simpson, N. R. W. (1948). *Brit. med. J.*, **1**, 545.
 Slot, G., and McDonald, A. D. (1947). *Ibid.*, **2**, 773.
 Stocken, L. A., and Thompson, R. H. S. (1941). Report to Ministry of Supply by Peters. Quoted by Peters, R. A., Stocken, L. A., and Thompson, R. H. S. (1945).
 Sulzberger, M. B., Baer, R. L., and Kanof, F. (1946). *J. clin. Invest.*, **25**, 474.
 Vey, F. (1941). Porton Report (Fairley). Quoted by Peters, R. A., Stocken, L. A., and Thompson, R. H. S. (1945).
 Waters, L. L., and Stock, C. (1945). *Science*, **102**, 601.
 Weatherall, M. (1948). *Practitioner*, **160**, 239.
 Wexler, J., Eagle, H., Tatum, H. J., Magnuson, H. J., and Watson, E. B. (1946). *J. clin. Invest.*, **25**, 467.

Le BAL (British Anti-Lewisite) dans le Traitement de l'Intolérance à l'Or**RÉSUMÉ ET CONCLUSIONS**

L'auteur passe en revue les recherches antérieures sur le BAL (*B*-chlorovinyldichlorarsine) et particulièrement celles qui ont trait à son utilisation chez les malades présentant des signes d'intolérance au traitement par l'or. Il décrit l'utilisation du BAL dans quinze cas de ce genre.

Le BAL semble être actif dans le traitement de l'intolérance à l'or. Dans la dermatite un trait marquant et constant est l'atténuation immédiate du prurit, et l'évolution de l'éruption est influencée dans un sens favorable. Le BAL est également actif dans le traitement de la stomatite et de l'hépatite provoquées par l'or.

Les réactions toxiques au BAL sont faibles pour des

doSES allant jusqu'à quatre milligrammes par kilogramme, excepté dans les cas d'hépatite pour laquelle il a été confirmé que le BAL doit être administré à des doses plus faibles si l'on veut éviter les réactions graves.

Dans la série citée ici on n'a pas constaté que l'administration de BAL ait fait réapparaître les symptômes d'arthrite rhumatismale.

On n'a pu aboutir à aucune conclusion au sujet de l'excrétion de l'or par l'urine à la suite du traitement par le BAL.

L'auteur formule des recommandations sur la posologie, en partie d'après les publications antérieures sur le sujet, et en partie d'après l'expérience limitée acquise avec la série de cas présentée ici. Il fait une distinction entre l'emploi du BAL pour le traitement des intolérances graves et celui des intolérances légères.