COPPER TREATMENT OF EXPERIMENTAL AND CLINICAL ARTHRITIS*

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Since 1940 copper salts have been used experimentally in the treatment of a variety of diseases. Goralewski (1940), Tüchler and Ranzenhofer (1940), and Arold (1940), used copper salts in the treatment of pulmonary tuberculosis. Forestier (1944, 1949), Forestier and Certonciny (1946, 1949), and Forestier and others (1948, 1950), popularized the use of organic copper salts in rheumatic diseases. Since the use of gold salts in rheumatoid arthritis carries the risk of toxic manifestations, it was desirable to find other chemical agents of lesser toxicity, and the copper salts were first used with this thought in mind.

The two principal organic salts of copper which have been used in rheumatic diseases are Cupralène† (m'allyl-cuprothiourea sodium benzoate) and Dicuprène‡ (cupro-oxyquinoline-diethyl-sulfonate). Cupralène is administered intravenously since its pH is 7.58; it contains 19 per cent. copper and is water-soluble. The usual dosage schedule is twice weekly (0.25 to 0.50 g.) with a total of 2 to 5 g. per series. Dicuprène contains 6.5 per cent. copper and is dispensed in an aqueous solution of pH 6.40; it may be given intramuscularly or intravenously (0.5 to 1.0 g.) 2 or 3 times weekly to a total of 6 to 12 g. per series.

Previous Investigations

Forestier and others (1950) claimed a beneficial response in rheumatoid arthritis of recent origin when copper salts were used therapeutically. He noted little toxicity and advocated their use as an adjunct in gold therapy for rheumatoid arthritis. His results were best in patients whose disease was of less than 1 year's duration and in whom copper salts constituted the initial therapy. When the duration of disease was less than one year, the clinical improvement was "greatly improved" and "moderately improved" in 72 per cent. of cases. When treatment was begun after the disease had been present for more than one year, only 40 per cent. were "improved" or "greatly improved". When copper was used

* These studies were aided, in part, by contract between the Office of Naval Research, Department of the U.S. Navy, and Stanford University (NR 131-202)—"Etiology and Treatment of Arthritis".

† Cupralène, manufactured by Société d'Expansion Chimique, Paris, was the gift of Merck and Co. Inc., Rahway, N.J., U.S.A.

‡ Dicuprène, manufactured by Union Chimique Belge, Brussels, was the gift of E. Fougere and Co., New York.

in patients resistant to gold therapy, only 21 per cent. were "improved" or "greatly improved". In those instances where copper was used after the patient had manifested an intolerance to gold, 50 per cent. "improved".

Tyson and others (1950) evaluated Cupralène in twenty patients whose disease had lasted one to 15 years, and in seven whose disease had lasted 2 months to one year. They reported no benefit in the first group with total doses ranging from 3.8 to 11.2 g. Two patients in the second group achieved remission but both relapsed in less than 6 months. They reported mild toxic effects, including transient, microscopic pyuria and albuminuria, occasional deep pain in the arm and shoulder following injection, thrombosis of the antecubital vein (in three instances), occasional nausea, vomiting, and chills, and several instances of anaemia which promptly returned to normal after discontinuing copper therapy. They also noted the garlic-like odour and taste experienced immediately after intravenous injection.

Forestier and Certonciny (1949) further reported the favourable effect of the organic salts of copper in chronic gouty arthritis. Graber-Duvernay and Van Moorleghem (1950) used an intravenous colloidal suspension of copper morrhuate in 117 cases of chronic rheumatoid arthritis and reported improvement in only 30 per cent. They noted little toxicity when using this suspension intravenously, but on intramuscular injection added procaine because of pain at the site of injection.

Present Studies

The purpose of our investigations was threefold: first, to evaluate Dicuprène and Cupralène in rheumatoid arthritis, rheumatoid arthritis with psoriasis, Reiter's syndrome, ankylosing spondylitis, and chronic gouty arthritis; second, to evaluate these substances in the experimental polyarthritis of rats; and third, to observe their toxic effects in man and rodents.

Evaluation in Treatment of Rheumatic Disease

Rheumatoid Arthritis.—Thirty-one patients (7 males and 24 females) were treated with a total dosage varying from 2.2 to 17.0 g. with injections given 2 or 3 times weekly (Dicuprène intravenously or intramuscularly, and Cupralène intravenously). Twenty-seven received Dicuprène and four Cupralène. The results are shown in Table I (overleaf), the patients being classified according to the extent of the arthritis and the degree of therapeutic response, according to the system outlined by Steinbrocker and others (1949) and advocated by the American Rheumatism Association.* Of the 31 patients treated, only six fell into Groups I and II and 25 were in Grades III and IV as judged by therapeutic response. Therefore, only 19.5 per cent. appreciably improved, fewer than Short and Bauer (1948) observed when only simple supportive therapy was used.

Psoriasis with Arthritis.—Among nine patients (2 males and 7 females) with psoriasis and associated rheumatoid arthritis, the number responding with Grade I or II improvement was 55.5 per cent. (see Table II, overleaf). In this group one patient received

* Grade I: complete remission.

Grade II: major improvement in which the sedimentation rate may still be moderately elevated but in which there is absence of systemic signs of activity such as leukocytosis and fever. There are no signs of joint inflammation although minimal changes due to irreversible capsular thickening may be present and no new rheumatoid process is present.

Grade III: minor improvement not considered significant since the disease has the inherent capability of variation in signs and symptoms. In this grade, however, are all those whose slight improvement prevents them from being Grade IV, and is yet so small that they cannot be Grade II.

Grade IV: no therapeutic response.

TABLE I
COPPER SALTS IN RHEUMATOID ARTHRITIS

Extent of Arthritis		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
I	1					
	2			2	3	5
	3	1				1
	4					
II	1					
	2	1	2	2	2	7
	3		2	2	1	5
	4				1	1
III	1					
	2			1	2	3
	3			1	1	2
	4					
IV	1					
	2			1	2	3
	3				2	2
	4				2	2
Total Patients		2	4	9	16	31
Percentage in each Grade		6.5	13	29	51.5	100

Only one case became worse.

Cupralène and the others, Dicuprène. No exacerbation of skin lesions was observed during treatment and generally they become less extensive.

Ankylosing Spondylitis.—Among three male patients with ankylosing spondylitis, the results of treatment with Dicuprène were not significant. One showed a therapeutic response of Grade I, a second Grade III, and a third Grade IV.

Chronic Gouty Arthritis.—In this group eighteen patients (16 males and 2 females) were treated. Eight (44.4 per cent.) showed a therapeutic response of Grade I or II; whereas 27.8 per cent. showed no appreciable improvement. Seventeen were treated with Dicuprène and one with Cupralène. These patients also continued to receive coated tablets of sodium salicylate, colchicine, and glycine (gelatin) daily, as they had been doing before the administration of copper salts, and they continued to complain of chronically swollen, painful joints and to have occasional acute exacerbations involving one or more joints. During the copper therapy, only one patient developed a severe exacerbation, and this was promptly controlled by cortisone. In the following year, six patients had acute exacerbations, but for the group generally, exacerbations have been less frequent and less severe. The results are shown in Table III (overleaf).

TABLE II
COPPER SALTS IN PSORIASIS WITH ARTHRITIS

Extent of Arthritis		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
I	1					
	2	1	1			2
	3					
	4					
II	1					
	2		1		3	4
	3		1		1	2
	4					
III	1					
	2		1			1
	3					
	4					
Total Patients		1	4	0	4	9
Percentage in each Grade		11	44.5	0	44.5	100

Seven of nine patients were females.

(It should be noted that the rating system for therapeutic response was devised for rheumatoid arthritis and its application in gouty arthritis is not to be compared with the series on rheumatoid arthritis but with other series on gouty arthritis.)

Reiter's Syndrome.—Three cases of Reiter's syndrome (2 males and 1 female) were apparently cured after the use of Dicuprène. In each of these, positive cultures for pleuropneumonia-like organisms were obtained from the conjunctivae and in the males from the penile sores and urethral discharge.

Disseminated Lupus Erythematosus.—Grade III response to Dicuprène (one case).

To sum up, Table IV (overleaf) shows that in rheumatoid arthritis the use of copper salts is apparently without benefit. In chronic gouty arthritis, the results are probably worthy of further study. In psoriasis with arthritis, a majority of cases showed improvement in arthritic manifestations and the skin lesions generally were ameliorated. In ankylosing spondylitis the results were insignificant. In Reiter's syndrome (a self-limiting disease), all cases responded favourably. In the one case of lupus erythematosus treated, the result was only slight improvement. Tables I, II, and III show that the patients who improved under treatment were in the less severe stages of each disease. Among those with rheumatoid arthritis treated with cortisone prior or subsequent to copper therapy, twelve out of fourteen had enjoyed a Grade I or II response and two had shown Grade III improvement; whereas under treatment with copper, one patient had a Grade I, two a Grade III,

TABLE III
COPPER SALTS IN CHRONIC GOUTY ARTHRITIS

Extent of Disease		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
Mild	1					
	2	2	3	1	1	7
	3					
	4					
Moderate	1					
	2				3	3
	3	1				1
	4					
Severe	1					
	2			1		1
	3			2	1	3
	4		2	1		3
Total Patients		3	5	5	5	18
Percentage in each Grade		16·6	27·8	27·8	27·8	100

TABLE IV
THERAPEUTIC RESPONSE TO ORGANIC COPPER SALTS
(Irrespective of Stage and Class)

Disease	No. of Cases	Per cent. Cases			
		I	II	III	IV
Rheumatoid Arthritis	31	6·5	13	29	51·5
Chronic Gouty Arthritis	18	16·6	27·8	27·8	27·8
Psoriasis and Arthritis	9	11	44·5	0	44·5
Ankylosing Spondylitis	3	33·3	0	33·3	33·3
Reiter's Syndrome	3	100	0	0	0
Lupus Erythematosus	1	0	0	100	0

and eleven a Grade IV response. This favourable therapeutic response to cortisone demonstrates the relative inferiority of the copper salts.

Clinical Toxicity.—The toxicity of these substances is slight.

Cupralène.—In all instances, the intravenous administration of Cupralène promptly resulted in garlic-like odour of the breath. This suggests its use in determining arm-to-lung circulation time, particularly since the garlic odour is not present before injection.

This odour persisted in some instances for as long as 8 to 10 hours after injection. If Cupralène escaped from the vein, intense pain and necrosis followed.

Dicuprène.—On intramuscular injection there was marked pain in many patients; so that in the later phases of the study this material was only given intravenously. There was no garlic-like odour of the breath. Three patients developed amenorrhoea while taking Dicuprène but menstruation was resumed after cessation of medication, and one became pregnant. This non-gravid amenorrhoea perhaps reflects an endocrine action.

Occasionally patients complained of slight, transient nausea after the injection of either Dicuprène or Cupralène. Transitory nausea and vomiting occurred in three patients, diarrhoea in one, vertigo in two, and increased stiffness in two. Pigmentation of the skin with pruritis occurred in one, and marked, transitory exacerbation of symptoms occurred in another after a single injection. The total number of reactions noted in relation to the large number of injections given in these groups of patients indicates a low order of toxicity. No change was noted in the blood counts or urinary findings on frequent examinations.

Experimental Arthritis.—An evaluation of Cupralène and Dicuprène was made in the experimental polyarthritis of rats. This arthritis was produced by the intraperitoneal injection of 2 ml. of a broth culture of the L₄ strain of the pleuropneumonia-like organism, as described by Tripi and others (1949). The rat polyarthritis is prevented or cured by the use of gold salts and is used in the laboratory as a means of comparing various substances with gold. Kuzell and Gardner (1950), and Kuzell and Mankle (1950), have indicated that terramycin and aureomycin will also prevent or cure this laboratory polyarthritis, but that various substances, including cortisone, ACTH, pregnenolone, and glutathione, will not prevent its development and even appear to aggravate its extent. Evaluation of the effect of the agents tested was made regarding per cent. survival, incidence of joint involvement, and extent of arthritic involvement scored numerically ("arthrogram score"*) for each group and its controls. The method of arthrogram scoring was described in this Journal by Tripi and others (1949). Since the pathogenicity of each sub-culture varies, it was necessary to run controls for each experiment. Further, the copper salts were tested for curative properties once the arthritis was at its peak, and for preventive properties when medication was begun at the time of the infection.

Cupralène.—Twenty male and twenty female 100-g. albino rats were infected, and beginning on the day of the infection half of each group was given 5 mg. per kg. body-weight of Cupralène intramuscularly for 2 days and thereafter twice weekly for 7 weeks. Among the treated animals, the incidence was 95 per cent., survival rate 70 per cent., and average arthrogram score (taken at the peak of the joint involvement) 3·5 for males and 3·0 for females. For the controls the comparable figures were 90 per cent., 45 per cent., 4·0 for males, and 3·1 for females.

* The "arthrogram" is a scoring device for calculating numerically the extent of joint involvement in the individual animal, using a scoring system based on 0 to 4 for each anterior extremity, and 0 to 5 for each posterior extremity, thus giving a possible score from 0 to 18. 0=no demonstrable signs of arthritis; 18=all four extremities involved to a maximum degree.

This method of scoring is purely arbitrary and is intended as a rough quantitative clinical estimation of macroscopic joint involvement. The average arthrogram score for the group is calculated by dividing the totals for the individual animals by the number of animals in the group. The averages are computed at various intervals so that the peak of joint involvement may be noted (see Tripi and others, 1949).

Ten male and ten female 100-g. albino rats were treated with 5 mg. per kg. bodyweight of Cupralène intramuscularly beginning the day of the infection, and thereafter 5 days per week to a total of eighteen injections. Among the treated rats the incidence was 95 per cent., survival rate 70 per cent., and average arthrogram score 6.45. Among twenty controls the comparable figures were 95 per cent., 45 per cent., and 6.95.

Ten male and ten female 100-g. rats were given 20 mg. per kg. Cupralène intramuscularly, beginning the day of infection, and thereafter twice weekly for 3 weeks. The incidence was 70 per cent., survival rate 100 per cent., and average arthrogram score 2.25. Among twenty controls the figures were 65 per cent., 100 per cent., and 2.9.

Twenty female 100-g. rats were given 5 mg. Cupralène intraperitoneally on the day after infection and twice weekly for 7 weeks. In the medicated animals the incidence was 80 per cent., survival rate 90 per cent., and average arthrogram score 3.3. In twenty female controls the comparable figures were 60 per cent., 100 per cent., and 2.5.

Dicuprène.—Nine male and ten female 100-g. albino rats were given 20 mg. per kg. bodyweight Dicuprène, and nine males and nine females were given 40 mg. per kg. bodyweight. Dicuprène intramuscularly beginning 11 days after infection and for 10 days thereafter. In the first group the incidence was 68 per cent., survival rate 95 per cent., and average arthrogram score 3.5. In the second group the figures were 83 per cent., 100 per cent., and 4.8. Among nine male and nine female controls, the comparable figures were 72 per cent., 100 per cent., and 3.2.

Eight male and nine female 100-g. albino rats were given 5 mg. per kg. bodyweight Dicuprène beginning on the day of infection and for 12 days thereafter, and nine males and nine females were given 10 mg. per kg. in the same manner. In the first group the incidence was 76 per cent., survival rate 100 per cent., and average arthrogram score 3.8. In the second group the comparable figures were 67 per cent., 54 per cent., and 2.2. In nine male and eight female controls, they were 54 per cent., 87 per cent., and 1.7.

Toxicity in Rats.—Using 347 albino rats of both sexes varying in weight from 100 to 300 g., the LD_{50} for Cupralène given intraperitoneally was found to be 160 mg. per kg. The intraperitoneal use of this material caused extensive adhesions.

The intramuscular administration of Cupralène caused considerable local necrosis and doubtless prevented complete absorption, since the LD_{50} by this method as determined in 45 rats was 375 mg. per kg.

For Dicuprène given intramuscularly the LD_{50} in 100-g. albino rats was 126 mg. per kg., based on administration of the material to fifty animals. There was little local reaction or apparent discomfort following the intramuscular use of Dicuprène.

Discussion

In our clinical experience we were unable to confirm the earlier reports of Forestier and his associates. We did note, however, that those patients showing improvement were generally among the early cases, as they also emphasized. We must keep in mind that these are the cases in which spontaneous remission is also most likely. Our results indicated, as did theirs, that in chronic gouty arthritis, the use of copper salts may be of value and merits further study. In spite of the fact that in rats the use of copper salts was ineffective against the pleuropneumonia-like organism, it was interesting that in three cases of Reiter's syndrome in which pleuropneumonia-like organism was cultured, the use of copper may possibly have effected remission. In the treatment of the arthritis associated with psoriasis the results suggested slightly more improvement than in rheumatoid arthritis without psoriasis, and perhaps here again the results merit further study.

As far as we know no evaluation of serum copper has been made in rheumatoid arthritis and in the studies of the use of copper salts no attention has been paid to this point. Dawson (1950) has studied "the copper protein, ascorbic acid oxidase", and observed that the enzyme copper undergoes a "reversible oxidation and reduction cycle only when the electron donor (ascorbic acid) and the electron acceptor (oxygen) are both present". Copper is also a constituent of tyrosine oxidases. The relationships among the different haemocyanins and their relation to copper proteins is not completely understood. Comar (1950) studied the tissue distribution of labelled copper administered to cattle, and found that the tissues showing high concentrations were, in decreasing order: "the liver, kidney, gastro-intestinal tract, adrenals, thymus, gall bladder, and bile." Cartwright (1950) reports that "the oxidation of glutathione, cysteine, ascorbic acid, and glucose is accelerated in the presence of copper", and that studies in copper deficient animals indicate that copper is "concerned in erythropoiesis, the process of myelinization of the central nervous system, and in the maintenance of normal mammalian pigmentation". It is also of considerable interest that Fay and others (1949) demonstrated that during normal pregnancy there is an increase in plasma copper. The increase begins in the first trimester and reaches maximum values (more than double the normal) during the last trimester, and in the first 2 months postpartum the plasma copper values regain their normal level. This period of rise in plasma copper levels parallels that of disappearance of symptoms of rheumatoid arthritis during pregnancy. The mere injection of organic copper salts in rheumatic patients will evidently not duplicate this suppression of symptoms, since undoubtedly the increase in plasma copper reflects a change in some other unidentified plasma to which the copper ion is bound.

Summary

(1) Organic copper salts are ineffective in preventing or curing polyarthritis of rats due to the L₄ strain of pleuropneumonia-like organism.

(2) The toxicity of organic copper salts in rats and mice was studied and the LD₅₀ found to be high.

(3) A clinical evaluation (using the scoring system advocated by the American Rheumatism Association) of Cupralène and Dicuprène was made in 31 cases of rheumatoid arthritis, three of Reiter's syndrome, three of ankylosing spondylitis, one of lupus erythematosus, eighteen of chronic gouty arthritis, and nine of psoriasis with associated arthritis. These compounds were of no value in the treatment of rheumatoid arthritis and ankylosing spondylitis. Three patients with Reiter's syndrome went into remission. There was questionable benefit in chronic gouty arthritis and in arthritis associated with psoriasis. One case of disseminated lupus erythematosus showed a Grade III therapeutic response. Generally, therefore, copper salts were found to be therapeutically ineffective.

(4) Toxic manifestations due to Cupralène and Dicuprène in 65 patients treated were infrequent, and of a mild, transitory nature.

(5) The garlic-like odour of the breath which follows intravenous administration

of Cupralène suggests its possible use in determining arm-to-lung circulation time.

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Traitement par Sels de Cuivre de l'Arthrite Expérimentale et Clinique

RÉSUMÉ

- (1) Les sels organiques du cuivre n'arrivent pas à prévenir ou à guérir la polyarthrite des rats causée par la souche L_4 du micro-organisme du type pleuro-pneumonique.
- (2) On a étudié la toxicité des sels organiques du cuivre chez le rat et la souris et on a trouvé que la DM 50 était élevée.
- (3) On a procédé à l'évaluation clinique (en se servant du système de notation préconisé par l'*American Rheumatism Association*) de Cupralène et de Dicuprène dans 31 cas d'arthrite rhumatismale, trois de syndrome de Reiter, trois de spondylite ankylosante, un de lupus érythémateux, 18 d'arthrite goutteuse chronique, et neuf de psoriasis compliquée d'arthrite. Ces produits étaient inefficaces dans l'arthrite rhumatismale et dans la spondylite ankylosante. Trois malades avec syndrome de Reiter ont eu une amélioration temporaire. Il y eut une amélioration douteuse dans l'arthrite goutteuse chronique et dans l'arthrite psoriasique. Un cas de lupus érythémateux disséminé a donné une réponse thérapeutique du troisième degré. Les sels de cuivre se sont donc généralement montrés thérapeutiquement inefficaces.
- (4) Des manifestations toxiques dues au Cupralène et au Dicuprène ont été rares, peu prononcées, et transitoires chez les 65 malades traités.
- (5) Une odeur d'ail de l'haleine se dégageant après l'administration intraveineuse de Cupralène fait penser à son emploi pour déterminer la durée de la circulation entre le bras et le poumon.

Tratamiento de la Artritis Experimental y Clínica por Sales de Cobre

SUMARIO

- (1) Sales orgánicas de cobre no son efectivas para prevenir o curar la poliartitis producida en ratas por organismos de la cepa L_4 del tipo pleuro-pneumónico.
- (2) Se ha estudiado la toxicidad de sales orgánicas de cobre en ratas y ratones y se encontró que la DL 50 era elevada.
- (3) Se ha procedido a la valoración clínica (según el sistema de anotación propuesto por la *American Rheumatism Association*) del Cupralène y del Dicuprène en 31 casos de artritis reumatoide, tres de síndrome de Reiter, tres de espondilitis anquilosante, uno de lupus eritematoso, 18 de artritis gotosa crónica, y nueve de psoriasis con artritis asociada. Estos compuestos no fueron efectivos en el tratamiento de la artritis reumatoide y de la espondilitis anquilosante. Tres enfermos con el síndrome de Reiter mejoraron temporariamente. Hubo mejoría dudosa en la artritis gotosa crónica y en la artritis asociada con psoriasis. Un caso de lupus eritematoso diseminado mostró una reacción terapéutica de grado tercero. Las sales de cobre son, pues, sin eficacia terapéutica.
- (4) Manifestaciones tóxicas debidas al Cupralène y al Dicuprène fueron raras, benignas y pasajeras en 65 pacientes tratados.
- (5) El olor del aliento con ressemblanza de ajos que sucede a la administración intravenosa del Cupralène sugiere su empleo para determinar el tiempo de circulación del brazo al pulmón.