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Photoreduction of Ferric Bleomycin

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The degradation of DNA by iron-bleomycin requires the formation of a complex with reduced oxygen species. Such complexes can result from reactions of Fe(III)·bleomycin with peroxides, or by reduction of O_2 with Fe(II)·bleomycin. In the absence of both peroxides and reductants Fe(III)·bleomycin is normally inactive in cleaving DNA, but, like Co(III)·bleomycin [1], some activity is detected upon exposure to strong light. This activity of the ferric complex is now shown to result from the formation of Fe(II)·bleomycin. Anaerobic solutions of Fe(III)·bleomycin, when exposed to ultraviolet light, produce a stable complex which forms a characteristic chromophore (λ_{max} = 500 nm) with the O_2-analogue ethyl isocyanide. This reacts with O_2 to cause DNA cleavage with the expected yield of ~20%, with the regeneration of Fe(III)·bleomycin as indicated by optical and EPR spectroscopy.

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Adsorptive Power of Different Activated Charcoal Samples of Some Metals at Various pH

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Activated charcoal still plays a very important role in toxicology [1–4]. Even though recent findings suggest that it might be replaced by more specific resins, charcoal will probably remain indispensible both as an aspecific external antidote, and as an internal antidote for haemoperfusion [5, 6]. One aspect which is still poorly understood is the adsorption of metals by charcoal because of the rarity of acute intoxications, the very high distribution volumes with low plasma levels, and difficulty in defining the chemical state of the solution. In spite of these limitations, our interest was focused on the adsorption of some heavy metals, *i.e.* Cd, Cu, Pb, and Zn. These metals are frequently the cause of occupational intoxications which very often show a chronic feature, though acute events can occur, and antidotal treatments generally are not sufficient. There is insufficient knowledge of the intermediate phases of heavy metal distribution and of the nature of the bonds these metals form with plasma carriers.

The aim of this study is to evaluate the adsorption of these ions by charcoal in water, before extending the research to the adsorption of the above-mentioned ions in plasma.

The charcoal samples were with or without coating; we pre-tested each for methylene blue adsorptive capacity according to *Ph. Eur.* [7] and assayed their 1 g/100 ml suspensions in 1 mg% w/v solutions of the four metals. The assays were done at 23 ± 1 °C pH 1.2–4.8 to avoid precipitation which can occur above pH 5. Adsorptive power was quantified after 5–15–30–60 min incubation by differential determination of each element by atomic absorption. The results showed that, as the pH increased within the narrow acidic range, the adsorption capacity of all charcoal samples was related to the increasing amount of complex ions of one or two OH^-. In particular, as the adsorption rate is dependent upon the physicochemical state of each metal at the above solution pH, Cd and Zn were least adsorbed because they are only in their Cd^{++} and Zn^{++} forms, whereas Cu and Pb were most adsorbed as the Cu^{++} and Pb^{++} forms are present only in traces.

Raw activated charcoal > 50 mesh showed higher adsorptive capacity than granulated charcoal coated with hydroxy-ethylmetacrylate (Norit). The coating material caused a 10–25% decrease in adsorption. A petroleum pitch based bead-type active carbon, of very hard 0.6 mm spherical beads and coated with collodion (Asahi Medical Co.), exhibited very high adsorptive power, almost comparable to the highest level exhibited by the raw activated crushed charcoal. In view of the effective detoxication and prevention of poisoning observed, the pH range studied seems to be large enough to permit an estimate of the adsorption power of raw charcoal in the gastric medium and to provide a preliminary evaluation of the use of covered charcoal in haemoperfusion. Finally the isotherms provide the desired metal:charcoal ratio to achieve the highest adsorption with the most suitable charcola. (See diags. on facing page).

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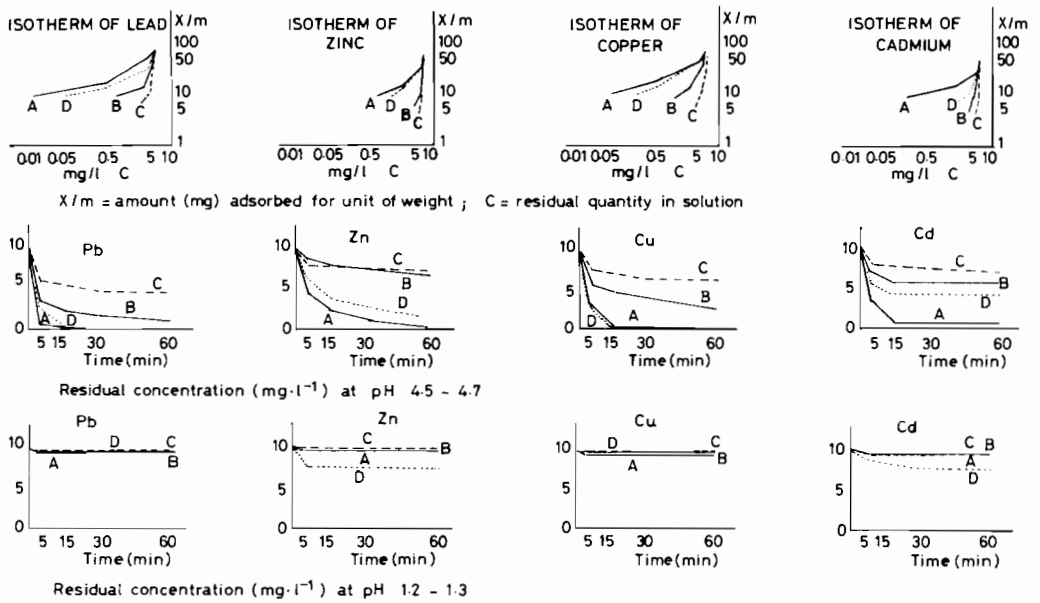

A = vegetable charcoal activated; B = granular vegetable charcoal activated; C = granular veget. charc. act. hy-1; D = charc. petroleum coated-collod.

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Anti-neoplastic Analogs of the Growth Factor Glycyl-L-histidyl-L-lysine–Copper(II)

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The human tripeptide, glycyl-L-histidyl-L-lysine (GHL) isolates from plasma as a copper complex (GHL-Cu). At nanomolar concentrations GHL serves as an *in vitro* growth factor for many types of cultured cells and organisms and appears to function by promoting copper uptake. *In vivo* GHL-Cu acts as an angiogenic factor that induces new capillary formation. The affinity of GHL for copper is approximately equivalent to the copper transport site on albumin [1, 2]. Physical studies have indicated that GHL chelates copper in solution to form a near-planar, tridentate, triaza three-ringed structure [2, 3].

Certain structural analogs of the GHL-Cu complex such as pyridine-2-carboxaldehyde-2′-pyridylhydrazone-copper(II) (PCPH-Cu) and salicylaldehyde-benzoylhydrazone-copper(II) (SBH-Cu) bind copper in an analogous fashion to form near-planar tridentate chelates [4]. Both PCPH-Cu and SBH-Cu are potent inhibitors of cell replication while free PCPH and SBH and their iron complexes are much less active. When tested on *in vitro* cultures of four cancerous cell lines, PCPH-Cu and SBH-Cu inhibit cell replication at concentrations approximately similar to that observed for the anti-neoplastic drugs *cis*-platinum or bleomycin (Table I). Human melanoma cells appear to be especially sensitive to PCPH-Cu.

In vivo, in the mice implanted with fibrosarcoma cells, after four weeks during which the test compounds were administered twice weekly into the tumor area, control animals had tumors averaging 1.5 cm^3 while SBH-Cu treated animals had average

TABLE I. Concentration of Anti-tumor Drug inhibiting DNA Synthesis by 50% in 4 Types of Cultured Neoplastic Cells.

Cell type	Drug concentration (ng/ml) for 50% inhibition			
	PCPH-Cu	SBH-Cu	*Cis*-platinum	Bleomycin
Mouse fibrosarcoma (MCA 1511)	0.50	11	2.4	32
Human bladder cancer (T-24)	12	34	95	7
Human lung epithelial cancer (SKMES-1)	580	410	870	44
Human melanoma (Effron)	0.052	70	6,000	80,000