M.Med. Thesis.

ACUTE DICHROMATE POISONING FOLLOWING THE USE OF TOXIC PURGATIVES.

R.WOOD B.Sc. B.M. B.Ch. D.T.M&H. F.C.P.(S.A.)

CONTENTS

INTRODUCTION

During the last ten years, several patients have presented to the Renal Unit of Groote Schuur Hospital with acute renal failure following the use of traditional (N'anga or Gqirha) medication. The history together with abnormal liver-function tests and renal failure was thought to be suggestive of a toxic aetiology. The specific toxin however remained unknown, until during the admission of one patient, a relative brought in the medication, analysis of which revealed a high concentration of potassium dichromate. Subsequently elevated levels of chromium were demonstrated by atomic absorption spectrometry in the blood and urine of this patient. Following this case there have been six further cases of acute renal failure resulting from use of dichromate containing traditional remedies. These remedies were obtained from a variety of sources including street-hawkers, herbal chemists, and traditional healers. Clinical and laboratory data relating to these seven patients will be presented.

The use of dichromate in traditional medicines is not limited to present-day Africa. In 1925 a young Indian woman died following the ingestion of a dichromate containing medicine prescribed by a travelling "Hakim" (1), and in 1940 two further deaths were reported in Uttar Pradesh Province, India after use of dichromate in traditional medicine (2).

Emetics and purgatives are commonly used in African tribal medicine (3). Traditionally enemas were dispensed via a truncated cow-horn, and consisted of vegetable material such as roots, herbs, tree-bark, and leaves. A recent series published from Baragwanath Hospital reported serious gastro-intestinal complications following use of "toxic enemas" and noted that they contained irritant substances such as Dettol chloroxylenol), vinegar, battery acid, potassium permanganate, copper sulphate and potassium dichromate (4). This latter substance is a mucosal irritant and it is this property which is being exploited by its incorporation into N'anga / Gqirha purgatives. Dichromate appears as the principal active ingredient of many

of the enemas that have been available for analysis. In contrast to metallic chromium which is biologically inert, dichromates containing hexavalent chromium are highly reactive with powerful oxidising properties. They are readily available, being used in a variety of industrial processes, including electro-plating, leather tanning and industrial and laboratory cleansing solutions. Hexavalent chromium is locally irritant to mucosal and epithelial surfaces. Topical exposure may lead to dermatitis and indolent mucocutaneous ulceration (5). Pulmonary exposure to chromic acid fumes may result in chronic bronchitis, interstitial pneumonitis, progressive pulmonary fibrosis and an increased incidence of bronchogenic carcinoma (6). Acute overdoses of chromium compounds, usually via the oral route and accidental, have only been infrequently described in the medical literature (7 - 22). The lethal oral dose of potassium dichromate can be as little as 0,5 - 1,0 gms (23), leading to acute tubular necrosis, gastrointestinal tract haemorrhage, hepatitis, haemolytic anaemia and encephalopathy. Little is known or has been published concerning the pathogenesis of dichromate toxicity. It will be shown that the toxicity of hexavalent chromium is related to its ability to readily penetrate cell membranes and its subsequent reactions with intra-cellular components. A hypothesis will be put forward that these intra-cellular reactions and in particular the presence of intra-cellular reducing agents are the determinants of organ injury by hexavalent chromium.

The literature relating to the use of radioactive chromium (Cr 51) as a label of red cells and plasma proteins will be reviewed. Data from this literature will be used to illustrate the effect of the valency state of chromium on its pharmacokinetics. Data relating to the body distribution of chromium will be presented in the form of post mortem tissue analysis from four cases of fatal dichromate poisoning.

Treatment regimens for dichromate poisoning remain largely unproven having been derived from animal studies together with only infrequent case reports. In particular there

is controversy in the medical literature concerning the effectiveness of dialysis in the elimination of body chromium. Dialysis and renal chromium clearance data will be presented and correlated with chromium concentrations in the red cell, plasma protein and plasma water compartments. The variable dialysability of each of these compartments will be put forward as a hypothesis to explain the apparently conflicting dialysis data in the literature.

CHEMISTRY

Chromium belongs to the first series of the transitional elements with an atomic number of 24 and a mass of 52,01. Chromium can occur in every oxidation state (valency) from -2 to +6, but only the ground states of 0, +2, +3 and +6 are common. The divalent compounds are only stable if protected from oxidation which takes place easily in air.

$$Cr^{3+} + e^{-} = Cr^{2+}, E = 410 \text{ mv}$$

Because of this very strong reducing power, divalent chromium compounds are unlikely to occur in biological systems.

The hexavalent forms of chromium are usually linked with oxygen, the two important ions being chromate ($Cr O_4^{2-}$) and dichromate ($Cr_2 O_7^{2-}$). Both chromate and dichromate are strong oxidising agents and can be reduced in acidic solutions to the trivalent form.

$$Cr_2 O_7^{2-} + 14 H^{+} + 6e^{-} = 2Cr^{3+} + 7 H_2 O, E = 1{,}33 \text{ V}$$

The hydroxyl groups of organic compounds are readily oxidised to ketones or aldehydes by this reaction. This can be observed when organic material contaminates dichromate containing cleaning solutions, the orange colour of dichromate changing to the characteristic green colour of trivalent chromium. The toxicity of hexavalent chromium is related to its solubility and this potential for oxidising organic material. As a result of this reaction the toxicity of dichromate containing medications can theoretically be affected in several ways. The presence of organic material or reducing agents in the medication could reduce the effective concentration of hexavalent chromium available for absorption. The time between mixing the ingredients and ingestion would also vary the extent to which this reaction could proceed and lastly the pH of the medication and gut contents would vary the rate of this reaction.

The trivalent form of chromium is the most stable of the various valency states and

Fig.1

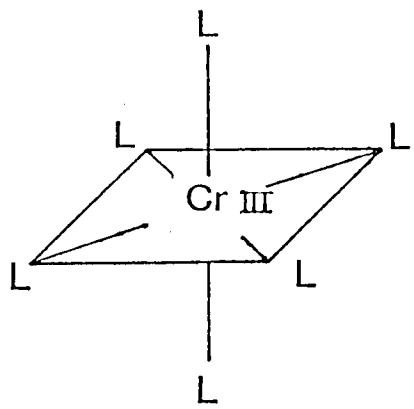
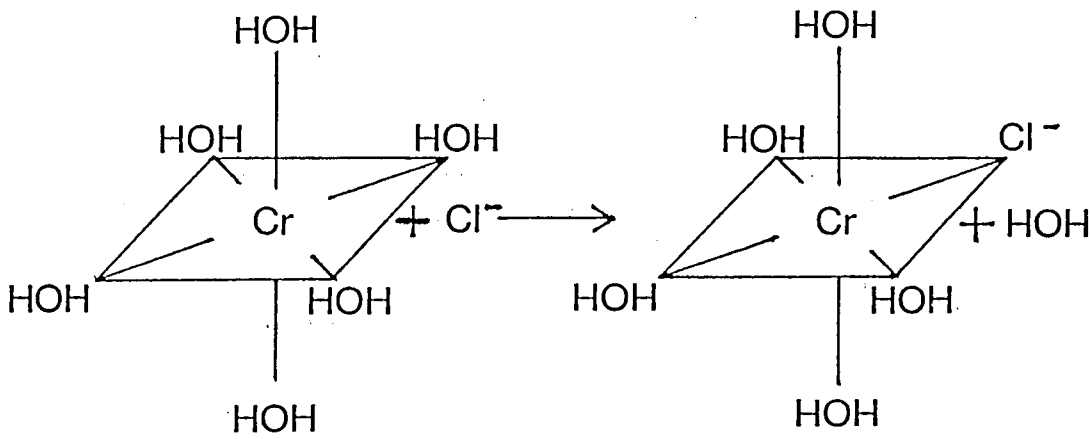

L
L
L
Cr III
L
L
L

Fig.2


HOH
HOH
HOH
Cr
+ Cl⁻
HOH
HOH
HOH
HOH
HOH
Cl⁻
Cr
+ HOH
HOH
HOH
HOH

characteristically has a strong tendency to form co-ordination compounds, complexes, and chelates. It is probably in the trivalent form that chromium is required as a trace element for glucose tolerance and as a structural stabilising factor for D.N.A. and R.N.A.. Trivalent chromium has a co-ordination number of 6 with the direction of the ligands pointing to the corners of an octahedron (Fig 1).

Common ligands include water, ammonia, urea (not charged) or anions such as halides, sulphate and anions of organic acids. Free chromic ion does not exist in aqueous solution; it is always co-ordinated with either water or other ligands in solution. These other ligands tend to replace the water so that mixed complexes (chelates) result (Fig 2). These complexes are stable at acid pH (<4) however as the concentration of hydroxyl groups increases, hydrolysis of the co-ordinated water results in co-ordination of hydroxyl groups (Fig 3).

Hydrolysis can also result in cross linkage between chromium molecules proceeding onto the formation of polynuclear complexes a process called olation (Fig 4). Olation is an important process in the chrome tanning of leather whereby trivalent chromium cross-links protein molecules.

If olation is allowed to proceed unhindered macro-molecular colloidal complexes precipitate out of solution and these complexes will be biologically inert. Simple trivalent chromium compounds are insoluble at neutral pH, however because of the strong propensity for olation, ligands capable of competing with hydroxyl groups are able to keep trivalent chromium in solution. Powerful ligands are able to displace hydroxyl groups and solubilise previously insoluble complexes. An example of this is seen when oxalate is used to detan leather. This property of powerful ligands may be important in dialysis where organic acid radicals are used in high concentration in dialysate as buffers. The lactate concentration of peritoneal dialysate is 45mmol/l and acetate concentration of haemodialysate is 35mmol/l.

Fig.3

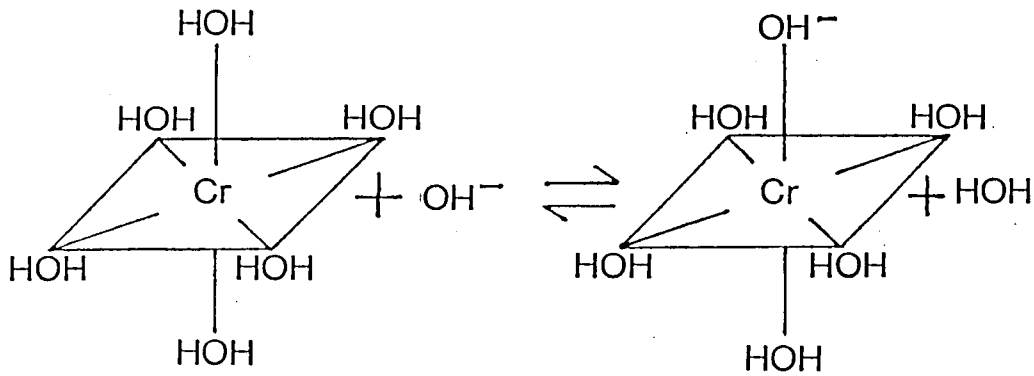
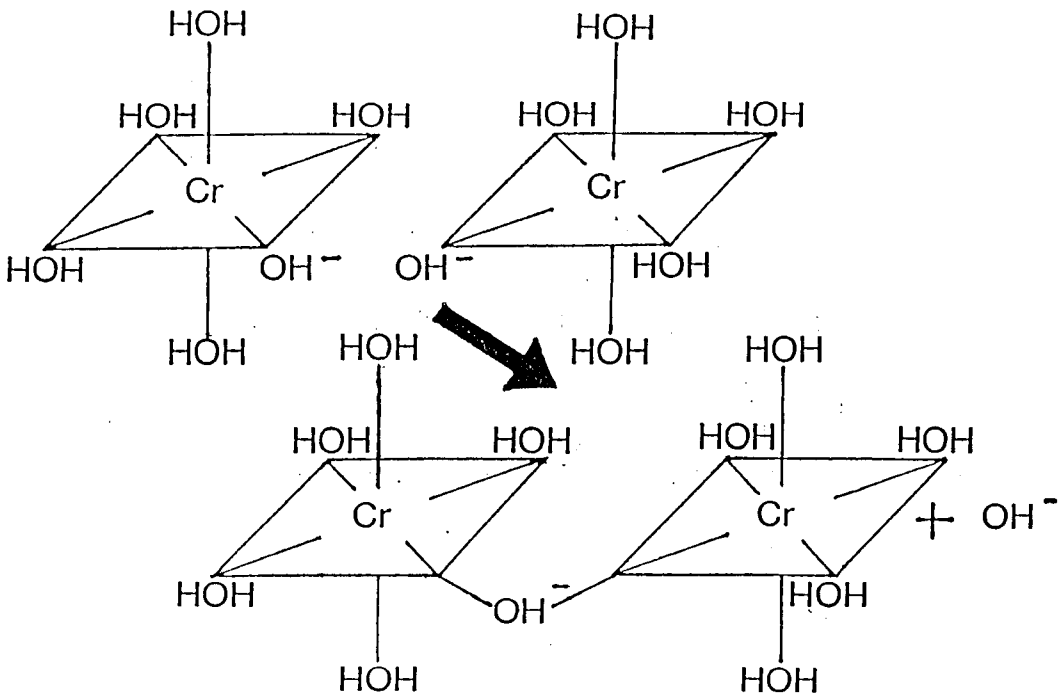

HOH
HOH
HOH
Cr
HOH
HOH
HOH
+ OH⁻
OH⁻
HOH
HOH
Cr
HOH
HOH
HOH
+ HOH

Fig.4


HOH
HOH
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Cr
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OH⁻
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Cr
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Cr
HOH
OH⁻
HOH
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Cr
HOH
+ OH⁻
HOH
HOH

Several aspects of the above chromium chemistry are of particular biological significance. The differences in oxidative potential between divalent and trivalent and between trivalent and hexavalent chromium are so great that reversible transition between the oxidative states is extremely unlikely to occur in biological systems. At physiological pH and in the presence of reducible radicals, hexavalent chromium will always tend to be reduced to the more stable trivalent form. The toxicity of hexavalent chromium results from both its solubility and the propensity to react with organic material especially by oxidising alcohol groups.

Simple trivalent chromium compounds are insoluble at physiological pH and are relatively biologically inert, however by means of olation and ligand exchange they can develop into both macro-molecular colloidal or soluble complexes. Soluble complexes with lactate or acetate are able to cross dialysis membranes and may be the form in which trivalent chromium is dialysable.

METABOLISM

ABSORPTION : Trivalent chromium is poorly absorbed from the gastro-intestinal tract; experimentally between 0,5% and 3% of an oral dose of chromic chloride is retained. Chromium is present in the diet in both inorganic and organically complexed forms. Experimentally chromium absorption is measured from total body counting after administration of Cr 51 or by urinary chromium output. Both these methods would underestimate absorption if significant excretion occurred via the gut as suggested by Hopkins (24). Visek et al (25) reported absorption of less than 0,5% of an oral dose of chromic chloride in the rat. Donaldson and Barreras (26) found that only 0,1-1,2% of an oral dose appeared in the urine of patients. A somewhat higher retention of 2-3% was recorded in rats receiving chromic chloride by stomach tube (27) and the intestinal absorption was independent of the dose given. The normal urinary chromium excretion in man of 2-6 micrograms/l with a diet containing an average of 80 micrograms (26) of the element would require an absorption of between 2,5 and 7,5%. Offenbacher and Pi-Sunyer (28) point out that chromium like other trace elements is subject to chemical interactions in the small bowel with both dietary (exogenous) and intestinal (endogenous) factors which may affect its absorption in various ways. Substances such as amino-acids chelate chromium in the small bowel and prevent it from precipitating at the alkaline pH of the intestine. Phytate decreases and oxalate increases chromium absorption in the rat. Diets high in simple sugars increase urinary excretion of chromium in humans.

Hexavalent chromium is a much less stable form of chromium which is not a normal biological constituent of the diet. Neither the site nor the mechanism of absorption is known. In view of the homology with sulphate and phosphate anionic radicals, chromates may be absorbed similarly. Donalson and Barreras reported (26) 2,1% absorption of chromate on the

basis of urinary excretion. Hanskey and Connell (29) utilised radio-active chromate as a non-absorbable tracer to estimate gut transit time, with less intestinal absorption than trivalent chromic chloride. By the nature of the marked toxicity of hexavalent chromium only small quantities can be used in absorption studies and under these circumstances the interaction with exogenous and endogenous factors is crucial, as chromate can rapidly be reduced to the insoluble trivalent form. Beyermann and Eschnauer (30) reported that when chromate was added to wine in concentrations of 0,1-50ppm (mg/l) it was completely reduced within 30 seconds. This effect can be overcome at higher doses of chromate, 100 mg/l retaining 2% chromate activity. Hanskey and Connell (29) administered the labelled chromate in tomato or orange juice, both of which could be expected to contain reducing agents such as ascorbic acid. Hexavalent chromium is soluble and readily penetrates cells and its absorption is determined by the extent of reduction which takes place by interaction with exogenous and endogenous reactants. This in turn is dependent on the dosage of chromate and the low pH of the stomach which predisposes to its reduction to the trivalent form.

TRANSPORT AND DISTRIBUTION

The application of radio-active labelling with chromium 51 (Cr 51) isotope to blood components has increased our knowledge of red cell and plasma protein survival and turnover. These techniques have also increased our knowledge of the body handling of chromium. With the development of high intensity isotopes these studies have used relatively small quantities of chromium compounds. It should be remembered that in the situation of high dosage, as in chromate toxicity, the normal binding mechanisms may be overwhelmed and organ distribution may not parallel these low dose experiments. Gray and Sterling in 1950 (31) described the labelling of red cells and plasma proteins with Cr 51. They noted that cationic trivalent chromium did not penetrate the intact red cell although it readily bound to free haemoglobin, this was felt to be a reflection of the relative impermeability of the red blood cell to cations. When mixed with serum in-vitro, chromic chloride bound to both the albumin and globulin fractions, the presence of chelating agents such as citrate inhibits this binding. The bond with albumin was very strong and able to resist prolonged dialysis without losing the chromium tag. Walker-Smith et al. (32) described in-vivo plasma-protein labelling with intravenous trivalent Cr 51, the binding was rapid and able also to resist dialysis. An early, large and unpredictable urinary loss of radioactivity (18-61%) was noted. This urinary chromium is dialysable, not protein bound and the renal clearance is related to the blood concentration of dialysable (non-protein bound) chromium not the protein bound fraction (33). Van Tongeren and Majoor (34) showed that the Cr 51 label on albumin shifted to untagged transferrin and that this translocation could be prevented by the addition of small quantities of ferric chloride. They concluded that the affinity of transferrin for iron was greater than for chromium. The in-vivo half-life of Cr 51 tagged albumin (6-9 days) was shown to be considerably less than that of iodine 131 (I.131) tagged albumin (21-24 days) and it was

postulated that because of the translocation of chromium to transferrin, the measured albumin half-life approximated to that of transferrin (8.7 days).

Hexavalent chromium (Cr VI) behaves very differently from trivalent chromium (Cr III), being taken up by red cells and subsequently reduced to the trivalent form within the cell. In-vitro this uptake is rapid with 98,3% of the Cr 51 uptake occurring within 25-45 minutes (35), the rate of uptake is diminished at a pH above 7,0 (36). The percentage of Cr 51 taken up by the red cell is not appreciably influenced by the amount of chromate ion present, within the range of 0,25-10,0 micro-grams per millilitre of blood. Within the red cell the chromium is in the trivalent form, bound to the Beta chain of the haemoglobin molecule (37). There is a small elution of approximately 1% per day of chromium from the cell but the remainder of the activity remains for the life-span of the red cell. Following cell death a proportion of the chromium appears in the urine in the trivalent form, the rest largely accumulates in the liver if the haemolysis is intravascular, or in the spleen if haemolysis is extravascular (36). During in-vitro labelling of red cells a small proportion of the hexavalent chromium is reduced to the trivalent form at the cell surface. If the cells are not washed prior to infusion, this chromium is rapidly excreted in the urine. With the use of high activity isotopes red cell survival is not shortened by the labelling technique, but at higher intracellular chromium concentrations, red cell metabolism is impaired. At an intracellular chromium concentration of 10 mg/l there is significant depression of glycolysis, at 5-25 mg/l glutathione reductase activity is inhibited, and above 22mg/l methaemoglobin concentrations rise (36). Visek et al. (25) administered small quantities of Cr 51 (50 micro-curies) to rats in the form of intravenous sodium chromate and chromic chloride. With sodium chromate the major uptake was by the liver with 25% of the activity deposited in that organ in 30 minutes after administration, and a urinary excretion of 35% in the first 4 days (Table I). Animals

sacrificed on day 4 had the highest tissue chromium concentration in the kidneys, with lower but significant amounts in the blood, liver, spleen and bone marrow. By contrast, after chromic chloride injection there were high concentrations in liver, spleen and bone marrow but low concentration in the kidneys. The only tissue which accumulated activity with time was the spleen, probably because of accumulation of red cell chromium. Danielsson et al (38) injected pregnant mice with much larger doses of Cr 51 (10mg/kg), in the form of intravenous sodium dichromate and chromic chloride (Table II). Again the same pattern is seen, with hepatic accumulation with both Cr III and Cr VI but high renal accumulation only with Cr VI. A modest placental transfer to the fetus was noted with Cr VI, but only minimal transfer with Cr III. Tsapakos et al. (39) injected rats with intraperitoneal sodium dichromate at high dosage (20 and 40 mg/kg) and again significant amounts of Cr were present in renal and hepatic tissue by 1 hour. The concentration in the nuclei reached a maximum at 4 hours with the 20 mg/kg dose and at 12-24 hours with the 40 mg/kg dose. The significance of this intranuclear concentration of Cr will be considered later in the discussion on the toxicology of Cr VI.

TABLE 1. **Taken from Visek et al.**

Summary of behavior of Cr 51 in rats following intravenous administration in different chemical forms.

	Na_2CrO_4	$CrCl_3$	$CrCl_3$ + Citrate
% in urine	35 (1,9)	15 (1,3)	75,1 (9,3)
Liver	,52 (,06)	5,5 (,69)	,31 (,12)
Spleen	,91 (,16)	3,2 (,35)	,76 (,28)
Kidney	2,1 (1,1)	,44 (,02)	,13 (,07)
Bone Marrow	,56 (,14)	1,5 (,23)	,13 (,08)
Blood	,52 (,07)	<,02	<,02

Tissue values are on day 4 post injection of 50 micro-curies Cr 51 and represent % of dose per gm of fresh tissue. Standard error in brackets (n=4).

Table II. **Taken from Danielsson et al.**

Comparison of concentrations of Cr 51 in rat fetuses and maternal organs 1 hour after intravenous injection of sodium dichromate or chromic chloride at dose of 10 mg Cr/kg.

	Cr VI	Cr III
Fetus	0,3 (,01)	0,03 (,002)
Liver	29,4 (2,2)	30,8 (6,5)
Kidney	38,1 (1,9)	5,3 (,7)
Serum	2,6 (,2)	9,3 (,9)

Concentrations are mg Cr/kg. Standard error in brackets (n=4).

EXCRETION

The main route for chromium excretion is renal, however there may also be a smaller intestinal loss. Visek et al. (25) using rats in metabolic cages reported a 20% faecal excretion after intravenous Cr III and 17% after Cr VI. Metabolic cages may not exclude urine contaminating faeces. Hopkins (24) reported a faecal excretion of 0,5-1,7% and avoided urine contamination of faeces by killing rats within a few hours of the administration of intravenous chromium. Enteric loss of plasma proteins has been studied in humans, using Cr 51 tagged proteins. Inflammatory bowel disease is associated with considerable intestinal protein loss. Walker-Smith et al.(32) using intravenous Cr III reported up to 17,1% faecal chromium in a patient with small bowel melanomatosis, but in the 9 control patients the faecal loss was less than 1% of the injected dose. Van Tongeren and Reichert (40) using a similar technique expressed intestinal protein loss as a clearance of Cr 51-labelled protein per unit of time. Patients without gastroenteropathy had plasma clearances of up to 13ml per 24 hours, whilst patients with protein-losing enteropathy had clearances of up to 600ml per 24 hours. These data demonstrate that in the normal human, the gut excretion of Cr III is minimal. There is little information concerning Cr VI intestinal excretion, but as gastroenteritis is a feature of Cr VI toxicity even if it is not taken orally (21), significant intestinal loss may be expected.

Renal excretion has been shown in both animals and humans to be the main route of chromium elimination. Visek et al. (25) reported that 35% of intravenous Cr VI and 15% of Cr III appeared in the urine of rats within 4 days. The urinary clearance of Cr III was greatly increased to 56% if the Cr III was administered with acetate and to 75,1% with citrate as a buffer. Walker-Smith et al. (32) noted that most of the urine loss of Cr III, occurring during in-vivo labelling of plasma proteins was in the first few hours. Collins et al. (33) showed in the dog, that after intravenous Cr III the dialysable portion of Cr decreased exponentially but the

renal clearance of dialysable Cr remained constant. This is an important concept as it follows that renal and dialysis clearances are not directly related to blood or plasma chromium concentration, but to the dialysable portion, which is that portion co-ordinated to small molecular weight ligands. There is very little protein-bound Cr excreted in the urine, most being in the dialysable form. Tubular reabsorption was approximately 63% of the amount filtered (33). Stable chelates such as Cr 51-labelled E.D.T.A. are not reabsorbed and can be used to accurately measure glomerular filtration rate (GFR.). Tubular reabsorption may account for the high concentrations of Cr found in renal tissue after exposure to Cr III however Cr VI has been shown to bind directly with proximal tubular cells without the need to be first filtered (41). As Cr VI is rapidly cleared from the serum by erythrocytes, hepatocytes, and proximal tubular cells it would be unlikely to appear in the urine for more than a few minutes after absorption, thereafter being in the more stable Cr III form. For example the early urine loss of Cr 51 seen after infusion of chromate tagged red cells is in the Cr III form (36).

TOXICOLOGY

Trivalent chromium is relatively non-toxic, with toxicity restricted to parenteral administration only. The lethal to therapeutic ratio is greater than 10,000 : 1, and the LD.50 of intravenous Cr III hexaurea chloride in rats is between 100 and 180 mg/kg (42).

Hexavalent chromium (Cr VI) is locally irritant to skin and mucosal surfaces and poses a significant occupational health hazard to chrome workers. The respiratory conditions reported include ulcers and perforation of the nasal septum, sinusitis, laryngitis, chemical pneumonitis, and bronchogenic carcinoma (6). Dermatological complications include contact dermatitis and indolent skin ulcers (chrome holes). An increased susceptibility to gastrointestinal inflammatory and ulcerative diseases has also been reported (43). Acute Cr VI toxicity is rare, reports in the medical literature are usually isolated in nature and following accidental ingestion or suicide attempts (7 - 22). Gastrointestinal complications following the use of toxic enemas have been reported from Baragwanath Hospital (44) and in two of their 11 patients it was suspected that the enemas contained dichromate. Seven cases of acute Cr VI poisoning are reported here following the use of toxic "traditional" remedies. Acute Cr VI toxicity is usually manifested by dysfunction of those organs in which Cr VI is preferentially concentrated. Clinically this includes hepatitis, severe gastroenteritis, acute renal failure and rarely haemolytic anaemia (16). The high uptake in these tissues can be explained by an uptake-reduction mechanism. At physiological pH Cr VI readily enters cells (35,45) and is subsequently reduced by cellular components such as the microsomal electron-transport cytochrome P-450 system (46) and glutathione (47). During the reduction process highly reactive intermediates may be formed, such as Cr IV and Cr V which subsequently bind to cellular structures. Cr V complexes have been demonstrated by electron spin resonance studies in cell cultures treated with Cr VI (48). The final reduction product of intra-cellular

Cr VI is the more stable Cr III, this intra-cellular conversion explains the uni-directional uptake of Cr VI by metabolically active cells. Tsapakos et al. demonstrated DNA inter-strand and DNA-protein cross-links in liver and kidney nuclei of rats exposed to intraperitoneal Cr VI (39). Similar nuclear lesions were seen in cultured chick hepatocytes exposed to Cr VI and these changes were parallelled by an inhibition of drug-mediated enzyme induction (45), an activity which requires both transcription and translation. Cupo and Wetterhahn (46) showed that DNA strand-breaks dramatically increased in Cr VI exposed hepatocytes when intracellular glutathione and P-450 levels were high and virtually disappeared when levels were low. These results suggested that metabolism of Cr VI by glutathione and cytochrome P-450 was required for DNA damage to occur.

Appenroth and Braunlich (49) reported that in rats given Cr VI subcutaneously, the predominant site of renal injury was the tubule, although at the peak of damage there was additional glomerular disturbance. The highest tissue concentrations of Cr are seen in the renal cortex of animals exposed to Cr VI (Tables I & II). Ellis et al. (17) reported the autopsy findings of a 22 month old infant dying 12 hours after Cr VI ingestion, the histological changes of acute tubular necrosis were seen and the renal tissue concentration of Cr was 51,9 mg/kg. It has been postulated that high renal Cr concentrations result from tubular reabsorption of Cr (42). However Collins et al. (33) reported in the dog that intra-venous Cr VI was rapidly reduced in-vivo and appeared in urine only in the Cr III state and renal tissue concentrations of Cr are much lower in animals exposed to Cr III than those exposed to Cr VI (Tables I & II, p16). Ruegg et al.(41) demonstrated in slices of rabbit renal cortex, that the cells of the convoluted proximal tubule were particularly sensitive to Cr VI. The sensitivity of these metabolically active cells to Cr VI may be the result of an uptake-reduction process similar to that seen in hepatocytes. Besides the direct toxic effect of Cr VI on renal cells,

patients with Cr VI poisoning may have other additive factors predisposing to acute tubular necrosis such as jaundice, blood loss, hypotension, haemolysis and infection.

The red cell intracellular reactions with Cr VI were discussed above (Transport of Cr). It was shown that at high Cr VI levels glutathione reductase was reduced and methaemoglobin increased, such cells have a reduced intravascular survival. Sharma et al. (16) reported a case of intravascular haemolysis in an 18 year old following Cr VI ingestion. Reticulocytosis, anaemia and hyperbilirubinaemia suggestive of haemolysis were noted in a case of Cr VI poisoning reported by Fristedt et al. (12).

Diarrhoea and vomiting are universally present in Cr VI poisoning and have been attributed to the known mucosal irritant properties of Cr VI. There has been only one case reported of Cr VI taken intravenously (21) and interestingly, nausea, vomiting and bloody diarrhoea were early clinical features. In case 7 reported below, severe colonic necrosis was seen at autopsy following oral ingestion of Cr VI, and in another 4 cases haematemesis was reported following rectal Cr VI. Intestinal mucosa may be damaged directly by intraluminal Cr VI and by blood-borne Cr VI.

CASE PRESENTATIONS

The following patients were all in-patients of Groote Schuur Hospital, Cape Town. between December 1979 to January 1990 and were referred to the Renal Unit of the Department of Medicine with unexplained acute renal failure. All patients were subsequently shown to have acute hexavalent chromium poisoning.

CASE 1 (N.M.)

This previously well 41yr old black male, a packer for a local company presented on 22/5/89 three days after self administration of an enema. The enema consisted of a cup of orange-red liquid which had been purchased from a township traditional healer as a purgative. He had been warned to expect some diarrhoea and vomiting. Soon after taking the enema there was the onset of diarrhoea initially orange-red liquid and subsequently frank blood mixed with a little stool. This was followed by vomiting of "coffee grounds", severe colicky abdominal pain and profound muscle weakness. Prior to admission he noted he was passing diminishing quantities of urine and developed dysphagia and hiccoughs.

EXAMINATION

General : Sick looking man, jaundiced, not anaemic, apyrexial, with generalised muscle tenderness, no oedema.

C.V.S. : Pulse 64/min, B.P. 150/80, Venous pressure 4cm, Heart sounds normal.

R.S. : Chest clear except a few fine crackles at both bases.

G.I.T. : Marked epigastric and right upper quadrant tenderness. No organomegaly. Stool occult-blood positive.

C.N.S. : Normal. Funduscopy normal.

INVESTIGATIONS

URINE : S.G. 1,010, Protein 2+, Blood 2+. Microscopy - Red and white cells 3+, broad granular casts and debris 4+.

C.X.R. : Normal.

A.X.R. : Normal.

E.C.G. : Normal.

Renal ultrasound : Normal sized kidneys, no obstruction.

HAEMATOLOGY : Hb.15,8gm/dl, HCT.0,48, MCV.87fl, WCC.12,3 Prothrombin INR.2,5.

BIOCHEMISTRY : Sodium 128mmol/l, Potassium 4,6mmol/l, Urea 27,8mmol/l, Creatinine 847micro-mol/l, Protein 74gm/l, Albumin 40gm/l, Calcium 2.13mmol/l, Phosphate 2,64mmol/l, Cholesterol 4,7mmol/l, Total bilirubin 42micro-mol/l, Conj.bilirubin 29micro-mol/l, Alk. Phos.169u/l, AST.1600u/l, ALT.2650u/L, CPK.357u/l, LDH.1967u/l. LDH.isoenzymes - LD 1 and 2 raised suggestive of intra-vascular haemolysis. LD 5 raised suggestive of hepatic or skeletal muscle damage. Blood digoxin level 1,4nmol/l.

ASSESSMENT AND MANAGEMENT

The patient provided us with a sample of the enema and this was shown to contain high levels of dichromate together with a digoxin-like substance. Subsequently therapeutic levels of digoxin and toxic levels of chromium were found in his blood. He was assessed as having acute renal failure as a result of dichromate induced tubular necrosis and required haemodialysis for 14 days. He remained oliguric until 1/6/89 when he began to pass increasing quantities of urine. The relatively elevated creatinine together with muscle tenderness raised the possibility of rhabdomyolysis however the CPK. was only modestly

raised and the LDH. isoenzyme pattern was not specific for muscle injury in the presence of such deranged liver enzymes. His hepatitis as evident by the raised enzymes and prolonged INR. settled with time and was not a clinical problem. Although intravascular haemolysis has been reported with dichromate poisoning and this patient had LDH.isoenzymes LD 1 and 2 raised, he maintained his haemoglobin with no increase in reticulocyte count. This patient has been lost to follow up. At the time of discharge his urea was 20mmol/l and creatinine 330micro-mol/l.

TABLE III

CHROMIUM : ATOMIC ABSORPTION SPECTROMETRY RESULTS (Case 1)

ENEMA FLUID : 6,250 mg/l (6,25 gm/l)

BLOOD & URINE : Day 2 - Whole blood pre-dialysis 3,7 mg/l

Whole blood post-dialysis 4,0 mg/l

Urine 5,4 mg/l

Day 6 - Whole blood 2,0 mg/l

Day 18 - Whole blood 1,1 mg/l

Urine 0,03 mg/l

CASE 2 (E.D.)

This 27 yr old black male labourer was admitted to another hospital on 23/11/79 with epigastric pain and haematemesis. He was noted to be oliguric and in renal failure. His haemoglobin dropped from 12 to 9gm/dl over ten days. He failed to respond to diuretics, became increasingly dyspnoeic and was transferred to this hospital on 3/12/79 in coma. The patient's uncle gave a history that two weeks prior to admission the patient had complained of low back pain and self-administered an enema made from an orange powder obtained from a local herbalist. Shortly afterwards he became ill and developed diarrhoea and vomiting.

EXAMINATION

General : Critically ill, pale, with a uraemic fetor, in coma, responding to painful stimuli only.

C.V.S. : Pulse 98/min, B.P. 100/70, J.V.P. 6cm, Gallop rhythm, peripheral oedema +.

R.S. : Tachypnoeic with bilateral crackles and wheezes.

G.I.T. : Normal.

C.N.S. : Encephalopathic but with no localising neurological deficit. Funduscopy normal.

INVESTIGATIONS

URINE : Protein 2+, Blood 2+. Microscopy : numerous red cells, occasional white cells and casts (granular and white-cell). Urinary protein 0,67gm/l (2.10gm/24hr). **Chromium 0,5mg/l.**

C.X.R. : Normal sized heart with bilateral pulmonary oedema.

HAEMATOLOGY : Hb 9gm/dl.

BIOCHEMISTRY : Sodium 143mmol/l, Potassium 3,5mmol/l, Urea 82mmol/l, Creatinine 2650micro-mol/l, Protein 62gm/l, Albumin 31gm/l, Calcium 1.96mmol/l, Phosphate 1,96mmol/l, Urate >0.80mmol/l, Total bilirubin 12 micro-mol/l, Conj.bilirubin 8 micro-mol/l,

Alk. Phos.370u/l, AST.>300u/l. **Chromium 2,7mg/l.**

ASSESSMENT AND MANAGEMENT

On admission this patient presented a clinical picture of acute renal failure with toxic encephalopathy and pulmonary oedema. Toxin ingestion was suspected and confirmed when the patient's uncle brought in some orange crystals which had been received as a herbal medicine. Analysis of this substance revealed it to be potassium dichromate and subsequent analysis of blood and urine confirmed toxic levels of chromium. After recovery the patient admitted having given himself a rectal enema of a solution of these crystals. On admission peritoneal dialysis was commenced and continued for 12 days with improvement in his mental state and pulmonary oedema. During this phase of his illness he was polyuric. At follow up 4 months later his urea and creatinine were in the normal range (urea 4,7mmol/l, creatinine 107micro-mol/l) and he had no serious sequelae from his illness.

CASE 3 (F.M.)

This 30yr old black male presented to his local Day Hospital on the 14/7/89 and was referred on to this hospital. His background history was that he was a married man with two children and employed as a storeman at a local retail store. There was no prior medical history of note and he had been completely well until one week before admission when he developed an evening headache. He took two proprietary analgesics and subsequently after his evening meal developed severe diarrhoea. This was initially dark black in colour but after three days he noted frank blood mixed with the stool. There was associated vomiting, initially of bile-stained vomitus and later of "coffee-ground" material. For three days before admission he had suffered constant epigastric pain which radiated through to his back, and had noted that his urine output was very scanty. During this period of time he consulted two general practitioners and received symptomatic treatment. He was asked directly about traditional remedies and denied either consulting a traditional healer or taking any other medication.

EXAMINATION

General : Sick looking man with a uraemic fetor, and frequent hiccoughing. Apyrexial with no pallor, adenopathy, clubbing, jaundice nor oedema.

C.V.S. : Pulse 90/min full volume, B.P. 160/100, Venous pressure not elevated, Apex beat not displaced and Cardiac auscultation normal.

R.S. : Increased rate and depth of respiration. Lungs clear.

G.I.T. : Soft, no organomegaly, bowel sounds present, with some epigastric tenderness. Rectal examination revealed soft brown stool which tested positive for occult blood.

C.N.S. : Normal. Funduscopy normal.

INVESTIGATIONS

URINE : Dipstix - S.G.1,010, Protein 2+, Blood trace. Microscopy - Leucocytes 3+, occasional hyaline and granular casts, debris 3+.

C.X.R. : No cardiomegaly, clear lung fields.

E.C.G. : Sinus rhythm at 75/minute, PR.interval 0,14 sec, QRS.axis +10, Left ventricular hypertrophy on voltage criteria.

Renal ultrasound : No obstruction but increased parenchymal echogenicity. Kidney size - right 11,8cm and left 11,6cm

HAEMATOLOGY : Hb. 15,6gm/dl, HCT. 0,41, MCV. 83,3, RBC. morphology normal. PLT. 296,0, WCC. 11,28. Differential - neutrophils 74%, lymphocytes 15%, monocytes 8%, eosinophils 1%, large unstained cells 2%. Westergren sedimentation rate 32mm/hr. Prothrombin INR. 0,9.

BIOCHEMISTRY : Sodium 123mmol/l, Potassium 5mmol/l, Urea 53,4mmol/l, Creatinine 1552micro-mol/l, Glucose 5,2mmol/l, Protein 68gm/l, Albumin 39gm/l, Calcium 2,18mmol/l, Cholesterol 6,7mmol/l, Urate 0,92mmol/l, Total bilirubin 5micro-mol/l, Conj. bilirubin 2micro-mol/l, LDH.(kinetic) 623u/l, AST. 44u/l, ALT.31u/L, Gamma GT. 45u/l, Amylase 268u/l.

ASSESSMENT AND MANAGEMENT

This man was assessed as being in acute renal failure due to acute tubular necrosis secondary to severe gastroenteritis and dehydration. Haemodialysis was commenced using minimal heparin in view of the history of gastrointestinal bleeding. Haemodialysis was continued for five days together with careful fluid and electrolyte management. Urine output increased and renal function improved, at follow-up six weeks later his serum urea was 5

mmol/l and creatinine 76 micro-mol/l. During his admission, following direct questioning he admitted visiting a local township Sangoma (traditional healer). On the day following the onset of headache he consulted the Sangoma, who mixed an enema in a tin can from a variety of ingredients in his consulting room and administered it rectally by means of rubber tubing. The charge for this consultation was R90. Within minutes of insertion of the enema there was onset of profuse diarrhoea and vomiting. Later he noted the stool to be plum coloured and the vomitus to be like "coffee grounds". Although the enema fluid was not available for analysis the diagnosis of hexavalent chromium poisoning was confirmed by the demonstration of toxic levels of chromium in both blood and urine. The urinary chromium concentrations and total daily excretion are given below together with blood and dialysate values.

TABLE IV

CHROMIUM : ATOMIC ABSORPTION SPECTROMETRY RESULTS.(Case 3)

URINARY CHROMIUM EXCRETION.

Day	24 hr VOL.	Cr Conc.	Total Cr
2	1550 ml	2,1 mg/l	3,3 mg
3	1200 ml	1,5 mg/l	1,8 mg
4	1530 ml	3,5 mg/l	5,4 mg
5	980 ml	0,75 mg/l	0,7 mg
6	1580 ml	0,45 mg/l	0,7 mg

24 hr Vol = 24 hour urine volume.

Cr conc. = Chromium concentration mg/l.

Total Cr = Total 24 hour urinary Chromium.

WHOLE BLOOD CHROMIUM LEVELS

Day 1 = 2,5 mg/l

Day 4 = 2,3 mg/l

Day 5 = 1,9 mg/l

TABLE V

ATOMIC ABSORPTION SPECTROMETRY RESULTS (CASE 3) cont.

Day 3	**Start of dialysis.**	**End of dialysis.**
RBC.Art.	3,3 mg/l	3,0 mg/l
RBC.V.	2,8 mg/l	3,0 mg/l
PLASMA.Art.	0,65 mg/l	0,5 mg/l
PLASMA.V.	0,65 mg/l	0,6 mg/l
Day 4		
BLOOD.Art.	2,2 mg/l	2,2 mg/l
BLOOD.V.	2,2 mg/l	2,3 mg/l
Day 5		
BLOOD.Art.	1,9 mg/l	1,7 mg/l
BLOOD.V.	1,7 mg/l	2,2 mg/l

Art. = Blood line leading to dialysis membrane.

V. = Blood line leading from dialysis membrane.

Values represent red cell, plasma and whole blood chromium concentrations in mg/l. at the commencement and at the end of 4 hours of dialysis. Day 3 was the third day of hospitalisation, 17/7/89 and was the second dialysis performed. Day 4 was the 18/7/89 and Day 5 the 19/7/89.

CASE 4 (V.S.)

A 47yr old mother of nine who worked as a domestic worker at City Park Hospital presented on the 27/12/87 with a 7 day history of bloody diarrhoea, with associated colicky central abdominal pain which was relieved by defaecation. She suffered from chronic constipation using laxatives regularly and had consulted a traditional healer for this problem. He had prescribed a yellow liquid and it was after the self-administration of about 50ml of this solution that her symptoms of vomiting and diarrhoea had started. Prior to admission she had noted the development of oliguria.

EXAMINATION

General : Apyrexial, no jaundice, no anaemia.

C.V.S. : Pulse 110/min, Venous pressure not elevated, B.P. 130/85 with no postural drop.

R.S. : Normal.

G.I.T. : Diffuse abdominal tenderness, no organomegaly, blood and mucus on rectal examination. Sigmoidoscopy : no ulceration but erythematous mucosa with small haemorrhages and contact bleeding.

C.N.S. : Fully alert with no neurological deficit.

INVESTIGATIONS

URINE : S.G. 1,010, Blood trace, Protein +. Microscopy - 5 wbc/hpf, numerous granular casts and debris. Urinary Electrolytes - Osmolality 227mosm/l, Sodium 60mmol/l, Potassium 18mmol/l, Urea 10,7mmol/l, Creatinine 1,9mmol/l.

C.X.R. : Normal.

Renal ultrasound : Both kidneys 14 cm, No obstruction.

HAEMATOLOGY : Hb 11,6gm/dl, WCC. 14,2, PLT. 403.

BIOCHEMISTRY : Sodium 107mmol/l, Potassium 5,8mmol/l, Urea 45mmol/l, Creatinine 1355micro-mol/l, Glucose 3,7mmol/l, Albumin 27gm/l, Calcium 1,48mmol/l, Phosphate 2,59mmol/l, Total bilirubin 7micro-mol/l, Conj. 2micro-mol/l, Alk. Phos. 115u/l, LDH.1148u/l (Isoenzymes LDH.1 AND 2), AST. 21u/l, ALT. 107u/l, GGT. 63u/l. Venous gases : pH 7,3, pCO2 3,7kp, pO2 5,7kp, Base excess -11,8,

ASSESSMENT AND MANAGEMENT

Due to the initial uncertainty of diagnosis a renal biopsy was performed which showed changes of acute tubular necrosis with tubular regeneration and a patchy interstitial infiltrate of polymorphs, lymphocytes and plasma cells. Subsequent analysis of the enema fluid revealed a high concentration of sodium dichromate (Chromium content by A.A.S. 40gm/l). The patient was assessed as having dichromate induced acute tubular necrosis and required haemodialysis until 13/1/88 (17 days). Inspite of good urine output, the slow rate of recovery of renal function was felt to be a bad prognostic sign and at follow up 24 months later significant renal impairment was still present (Urea 9mmol/l and Creatinine 155micro-mol/l). The elevated LDH. together with the isoenzyme pattern were suggestive of haemolysis and the haemoglobin subsequently fell to 6,5gm/dl, requiring a transfusion of three units of packed

cells on 13/1/88. Abdominal symptoms and liver function tests rapidly normalised.

Attempts to contact the prescriber of the enema were unsuccessful and the patient refused to bear witness against him.

CASE 5 (J.N.)

This 37yr old black male presented to this hospital on the 2/11/89 four days after the self administration of an enema. He admitted to being a regular user of such enemas, this one having been purchased from a township traditional healer. Immediately post administration he experienced the acute onset of severe burning lower abdominal pain followed by bloody diarrhoea and vomiting. The diarrhoea continued until the day before admission when the stool became yellow and mucoid. He reported that he had been totally anuric for 36hrs and his admission was precipitated by exacerbation of the abdominal pain.

EXAMINATION

General : Alert and fully orientated. Apyrexial, no jaundice, pallor nor oedema.

C.V.S. : Pulse 100/min, B.P. 170/95, Venous pressure not elevated, Cardiac auscultation normal.

R.S. : Normal

G.I.T. : Diffuse tenderness, bowel-sounds present, generalised peritonism with rebound tenderness. Rectal examination revealed yellow mucoid stool which tested positive for occult blood.

C.N.S. : No neurological deficit. Funduscopy normal.

INVESTIGATIONS

URINE : Not available.

C.X.R. : No cardiomegaly, clear lung fields.

A.X.R. : Non specific ileus pattern and no free gas.

HAEMATOLOGY : Hb. 13,7gm/dl, HCT. 0,36, MCV. 83fl, PLT. 153, WCC. 16,16.

BIOCHEMISTRY : Sodium 128mmol/l, Potassium 5,1mmol/l, Urea 49,5mmol/l, Creatinine 1115micro-mol/l, Protein 50gm/l, Albumin 27gm/l, Calcium 1,83mmol/l, Phosphate 2,02mmol/l, Cholesterol 3,5mmol/l, Urate 0,58mmol/l, Total bilirubin 14micro-mol/l, Alk.phos 118u/l, LDH.980u/l, AST. 18,u/l, ALT. 65u/l, GGT. 35u/l.

ASSESSMENT AND MANAGEMENT

This man was suspected of having taken a dichromate containing enema and this was confirmed by finding toxic levels of chromium in his blood. His renal failure was managed by fluid and electrolyte restriction together with haemodialysis. Dialysis was performed via bilateral femoral vein catheters with minimal heparin use. Urine output improved over the following days and dialysis was discontinued on day ten. At follow-up two months later the urea and creatinine had returned to normal levels. His abdominal pain and diarrhoea were slow to settle, and he required a transfusion of two units of packed cells on the 6/11/89.

The urinary chromium excretion together with blood and dialysis data are given below.

TABLE VI ATOMIC ABSORPTION SPECTROMETRY RESULTS (CASE 5)

Day 1	Start of dialysis.	End of dialysis.
BLOOD	6* mg/l	3,8* mg/l
PLASMA	3,4 mg/l	1,9 mg/l
PLASMA WATER	2,6 mg/l	1,1 mg/l
DIALYSATE	0,1 mg/l	0,05 mg/l
Day 2		
BLOOD	4* mg/l	4* mg/l
PLASMA	2,8 mg/l	1,7 mg/l
PLASMA WATER	1,17 mg/l	0.3 mg/l
DIALYSATE	0,07 mg/l	0,05 mg/l

Values represent Chromium concentrations at the start of haemodialysis and at the end of 2 hours of dialysis on Day 1 (2/11/89) and 4 hours on Day 2 (3/11/89). Plasma water is the ultra-filtrate of plasma using a Baxter 15:11 hollow fibre membrane. * There were technical problems ashing these samples.

URINARY CHROMIUM EXCRETION

Day	24 hr Vol.	Cr conc.	Total Cr
5	220 ml	12,5 mg/l	2,8 mg
6	305 ml	11,3 mg/l	3,4 mg
7	1440 ml	5,8 mg/l	8,4 mg
8	1650 ml	5,6 mg/l	9,2 mg
9	2000 ml	4,7 mg/l	9,4 mg

Cr conc. = Chromium concentration mg/l.

Total Cr = Total urinary Chromium.

CASE 6 (D.M.)

This 22yr old black male was previously quite well and attending school in Transkei when in February 1989 he developed episodes of psychotic behavior. This prompted his mother to bring him to Cape Town where his father was employed and they placed their son in the care of a local township traditional healer. Whilst under his care, he was given an enema which evidently caused some rectal trauma as he recalls passing blood but no stool. Over the next few days he was given oral medicines which resulted in profuse diarrhoea and his subsequent admission to this hospital on the 8/8/89.

EXAMINATION

General : Toxic looking young man, dehydrated, hypothermic, shocked and unable to give an account of himself. Ulcerations involving the corners of the mouth and the buccal mucosa extending to the pharynx. The ulcers were noted to have dry looking leathery bases. The tongue was inflamed and swollen.

C.V.S. : Pulse 96/min, B.P. 120/70, Heart sounds normal.

R.S. : Acidotic breathing. Lung fields clear.

G.I.T. : Soft, no organomegaly. Posterior to the anus there was an area of skin necrosis and there was an offensive discharge.

C.N.S. : Confused but with no localising neurological deficit. Tendon reflexes were brisk bilaterally.

INVESTIGATIONS

URINE : Microscopy - Red cells 3+, broad granular casts and debris.

C.X.R. : Normal.

A.X.R. : Dilated small loops of bowel, no obvious obstruction.

HAEMATOLOGY : Hb. 9,2gm/dl, WCC. 53,000, PLT. 316, Prothrombin INR. 1,3, PTT. 28.

BIOCHEMISTRY : Sodium 114mmol/l, Potassium 5,4mmol/l, Chloride 80mmol/l, Urea 82,8mmol/l, Creatinine 1100micro-mol/l, Protein 60gm/l, Albumin 26gm/l, Calcium 1,73mmol/l, Phosphate 2,53mmol/l, Cholesterol 3,9mmol/l, Urate 0,94mmol/l, Total bilirubin 9micro-mol/l, Conj.bilirubin 2 micro-mol/l. Kinetic Enzymes - CPK.1324u/l, LDH.1004u/l, AST. 40u/l, ALT. 8u/l. Blood gases - pH7.13, pCO2 1,8kp, pO2 20kp, Base excess -23, Standard bicarbonate 7,4.

BACTERIOLOGY : Blood cultures positive for Streptococcus pneumoniae and Proteus mirabilis.

ASSESSMENT AND MANAGEMENT

After initial resuscitation he became polyuric, and was assessed as being septicaemic in non-oliguric renal failure with a severe metabolic acidosis. Haemodialysis was required for the first week, although he never became anuric. His blood urea and creatinine levels steadily improved, normalising about 8 weeks after admission. Initial management included broad spectrum antibiotics, ventilation and parenteral nutrition. This patient required multiple surgical procedures. On 30/7/89 an area of necrotic skin 4 cm by 2 cm posterior to the anus was debrided and a necrotising fasciitis-like slough was found to extend upwards between the rectum and sacrum as far as the sacral promontory, requiring extensive tissue excision including the levator ani muscles. A perforation of the posterior anal canal was noted, and a defunctioning colostomy was performed. Three days later a second debridement was carried

out when further necrotic tissue was excised from the retroperitoneal area of the pelvis. Two major haemorrhages occurred from the pelvic cavity which required suture ligation of the bleeding vessels.

Blood chromium level was elevated in the toxic range (**3,0 mg/l**). It was presumed that this patient had an enema which damaged the rectum with possible extravasation of enema contents complicated by further necrotising fasciitis from secondary infection. He most likely was also given dichromate orally causing the oropharyngeal ulceration and diarrhoea, with the absorbed hexavalent chromium being an additive causative factor in the development of acute tubular necrosis.

He was left with impaired bladder control; without sensation of bladder filling and no control over urination. A cysto-metrogram showed features of both an upper and lower motor neurone bladder. This has been managed by intermittent self catheterisation. The pelvic wound was slow to heal and he has been left with a permanent colostomy. Neurological assessment failed to find any cause for his initial neurological condition and there were no further episodes of psychotic behavior. There was full recovery of the oral ulceration, and renal dysfunction resolved.

CASE 7 (W.P.)

A 48yr old black male labourer at an explosives factory was treated on the 18/10/85 at the company hospital with parenteral penicillin for gonorrhoea. One week later he was admitted to the same hospital with diffuse abdominal pain, bloody diarrhoea, vomiting and oliguria. On admission he was noted to be pyrexial, jaundiced and anuric. It was known that he had taken a traditional remedy for venereal disease immediately prior to admission, taking this medicine orally rather than as an enema or topical application. The medicine had been purchased in Guguletu earlier for R50. He was transferred to this hospital on the 28/10/85 and the medication was sent along with him. It was an oily liquid with an orange hue which turned green on the addition of acid ; bench-top analysis demonstrated a high concentration of dichromate and potassium in the mixture.

EXAMINATION

General : Distressed, markedly jaundiced, apyrexial and no pallor nor oedema.

C.V.S. : Pulse 100/min, B.P. 115/70, Venous pressure 5cm, Heart sounds normal with a 2/6 ejection systolic murmur.

R.S. : Normal.

G.I.T. : 8cm tender hepatomegaly, additional lower abdominal tenderness, stool occult-blood positive.

C.N.S. : No abnormality. Funduscopy normal.

INVESTIGATIONS

URINE : Not available.

C.X.R. : No cardiomegaly, clear lung fields.

A.X.R. : Dilated loops of small bowel with multiple fluid levels and a right upper quadrant mass consistent with an enlarged liver.

E.C.G. : Normal.

Renal ultrasound : Normal sized kidneys with increased echogenicity.

HAEMATOLOGY : Hb. 11,6gm/dl, HCT. 0,35, MCV.77, PLT. 213, WCC. 9,3. Differential normal with no left shift. Prothrombin INR. 2,3.

BIOCHEMISTRY : Sodium 121mmol/l, Potassium 6mmol/l, Urea 40mmol/l, Creatinine 986micro-mol/l, Bicarbonate 12mmol/l, Protein 70gm/l, Albumim 31gm/l, Calcium 1,78mmol/l, Phosphate 4,03mmol/l, Urate 0,85mmol/l, Total bilirubin 171 micro-mol/l, Conj. 142micro-mol/l, Alk Phos. 205u/l, LDH. 2740u/l.

GASTROSCOPY : Oesophagitis with friable necrotic tissue but no active bleeding and no varices. There were petechial haemorrhages in the stomach with contact bleeding. No peptic ulcer seen.

SIGMOIDOSCOPY : Normal.

BACTERIOLOGY : Viral screen (incl. Hep B, VDRL.) negative. Blood cultures and Leptospirosis serology negative.

ASSESSMENT AND MANAGEMENT

This man was assessed as being in oliguric acute renal failure together with hepatic failure and gastro-intestinal necrosis secondary to oral dichromate ingestion. Peritoneal dialysis was commenced but discontinued because of technical problems. Daily haemodialysis via bilateral femoral vein catheters was started on day 4 (31/10/85) and continued until day 24 (20/11/85). Charcoal haemoperfusion was performed on days 6,7,and 8. Liver failure was treated with Lactulose, oral neomycin and parenteral vitamin K. In view of his gastro-intestinal pathology he was kept nil by mouth and parenteral nutrition was commenced on day 3. On day 3 intubation and ventilation were required because of deteriorating respiratory function. Initially he was haemodynamically stable, however from day 5 onwards he developed increasing rectal blood loss. The stool was maroon in colour and two to four units of blood were required daily to maintain his haemoglobin. The patient remained lucid and conscious, his jaundice resolved and hepatic function improved although gastrointestinal blood loss continued. On day 10 hyperglycaemia was noted and Candida albicans was cultured from blood, urine, and stool. Cultures remained positive despite parenteral amphotericin B. Following a large haematemesis on day 23, a repeat gastroscopy showed an erosive oesophagitis with active bleeding. A Sengstaken balloon was used but failed to control the bleeding. The following day (29/11/85) the patient became bradycardic and died.

POST MORTEM FINDINGS

There were extensive changes in the gastrointestinal tract with erosions and necrosis of the oesophageal mucosa, gastritis and mucosal desquamation and necrosis throughout the colon. The kidneys were large and pale, with numerous small cortical abscesses filled with

Candida, and there was evidence of widespread tubular damage. The liver was homogeneously enlarged. Because of considerable autolysis further histological analysis was not performed. Analyses of the chromium content of the traditional medicine, blood samples and post mortem tissues are given below.

TABLE VII

ATOMIC ABSORPTION SPECTROMETRY RESULTS (Case 7)

ADMISSION RESULTS.

Whole Blood Chromium : 2,0 mg/l

Serum Chromium : 0,4 mg/l

Urine Chromium : 2,0 mg/l

SERUM CHROMIUM CONCENTRATIONS.

Day 1 : 0,4 mg/l

Day 2 : 0,5 mg/l

Day 9 : 0,4 mg/l

Day 12 : 0,5 mg/l

Day 17 : 0,4 mg/l

Day 19 : 0,3 mg/l

POST MORTEM CHROMIUM ANALYSIS.

ORGAN	CHROMIUM CONC.	TOTAL CHROMIUM
Liver	45,0 mg/kg	96 mg
Kidney	10,0 mg/kg	5 mg
Stomach	- - - -	3 mg
Intestine	0,3 mg/kg	4 mg
Brain	0,3 mg/kg	2 mg

CASE DISCUSSION

Complications following tradition enema usage have been documented in a series reported from Baragwanath Hospital (44). Of their 11 reported cases, 2 (one suspected and one definite) followed the use of dichromate containing enemas. Both of these patients suffered gastrointestinal mucosal ulceration, however renal failure and hepatic dysfunction were not reported features. In each of the 7 cases documented above, the clinical features were compatible with the known toxic effects of acute dichromate poisoning, blood chromium levels were demonstrated well into the toxic range and where the medication administered was available, dichromate was in high concentration and the major active ingredient. All our patients were young black adults with an age range from 22 - 48 years (mean age 36 yrs), and there was only one female (case 4). Six patients took the medication as an enema, one orally (case 7), and one appeared to have been given both oral and rectal medication (case 6). The delay between taking the medication and presentation at hospital was from 3 and 7 days in all patients except case 7, who was reported to have taken oral medication immediately before hospitalisation. All our patients had renal failure but there was also a markedly variable pattern of hepatic and gastrointestinal involvement. At presentation all gave a history of abdominal pain, gastro-intestinal haemorrhage and oliguria. In cases 2, 3, and 4, the abdominal symptoms had largely resolved and the clinical picture was of unexplained acute renal failure. In cases 5, and 6, abdominal symptoms predominated, in case 1 there was hepatic failure, and in case 7 all three organ systems were involved.

All the cases (except case 6 who was non oliguric) presented with acute oliguric renal failure requiring dialysis. Dialysis was performed for between 7 and 26 days, the length of this period being determined by the clinical status of the patient and the rate of recovery of renal function. The urine findings were consistent with a diagnosis of acute tubular necrosis, as was

the renal histology in case 4. Other factors predisposing to acute tubular necrosis were present in 3 patients, including sepsis, dehydration and jaundice. The serum creatinines before dialysis were very much higher (range 847 - 2650 micro-mol/l) than usual in patients with acute renal failure of only a few days duration, an observation that has been previously noted in Cr VI toxicity (21). This is suggestive of, 1: acute on chronic renal failure, 2: rhabdomyolysis or 3: a hypercatabolic state. Lack of the clinical stigmata of chronic renal disease together with recovery of function would exclude chronic renal failure. Rhabdomyolysis has not been described in animals exposed experimentally to Cr VI, and muscle tissue does not accumulate Cr (25). In cases 1 and 6 serum creatine phosphokinase (CPK.) levels were markedly elevated at 357u/l and 1324u/l respectively. The local muscle necrosis in the rectal lesion of case 6 would adequately account for his elevated CPK. On the other hand in case 1, the presenting symptoms of profound muscle weakness together with some muscle tenderness are more suggestive of a myopathic element. This still does not necessarily implicate Cr VI as a causative factor, as other metabolic derangements can predispose to rhabdomyolysis, such as hypokalaemia and hypomagnesaemia following extensive vomiting and diarrhoea. In all the cases, although the serum creatinines were very high they were not disproportionate to the serum ureas as would be expected in rhabdomyolysis. It is most probable that these patients were very hypercatabolic. Acute haemodialysis of patients with Cr poisoning usually poses no significant problems except cognisance must be taken of the possibility of exacerbating gastrointestinal haemorrhage if heparin is used to prevent clotting on the dialyser membrane. This can be avoided by using no or minimal heparin and maintaining high flows across the dialysis membrane via bilateral femoral vein catheters. Peritoneal dialysis is a viable alternative.

Hepatic involvement was particularly variable with two of the patients presenting with

jaundice, markedly raised transaminases and very prolonged prothrombin times, whilst three other patients had near normal transaminases and bilirubin values. Bader (21) reported normal transaminases in a patient following intravenous chromic acid and postulated that this may have been due to absence of a first highly concentrated pass though the portacaval system. Transaminase values after oral ingestion of Cr VI have varied from normal (16), to mildly elevated (17,20) and up to levels of AST. and ALT. of 4400u/l (14). In our cases bilirubin values paralleled those of the transaminase levels. Alkaline Phosphatase levels were mildly elevated in all cases when measured (6 cases). The maximal derangement of liver function tests was at the time of admission, with subsequent normalisation in every case. This is compatible with a single toxic insult at the time of Cr VI ingestion. The variable susceptibility to hepatic injury has not been previously addressed. The first-pass phenomenon may indeed be a significant factor, Visek et al. (Table 1) showed a lower liver concentration of Cr relative to the kidney after intravenous Cr VI than did Danielsson et al. after intraperitoneal Cr VI (Table 2). However all our patients took Cr VI via the gut, and would have been exposed to high portal vein concentrations. It could be postulated that the rate of absorption was variable, thus exposing the liver to lower portal vein Cr VI concentrations, and allowing greater uptake by red cells. Red cells are competing for the Cr VI in the portal vein, however the rate of uptake has been shown by Mollison and Veall (35) to be independent of Cr VI concentration, within the range of 0,25 -10mg/l. Another interesting hypothesis could be that the variable hepatic injury results from differing activity of intracellular hepatic enzymes such as P-450 and glutathione reductase, the in vivo parallel to the in vitro studies of Cupo and Wetterhahn (46,47).

LDH. values were universally raised, and in case 1, iso-enzymes were of haematological and liver or muscle origin. In case 4 the iso-enzyme pattern was suggestive of a haematological

source. In the clinical situation of liver, renal, gut and possible red cell injury, iso-enzyme patterns are difficult to interpret.

Gastrointestinal symptoms were present in all our cases, and was the precipitating cause of the death of case 7. Mucosal inflammation and ulceration of the respiratory tract has been reported after occupational exposure to Cr VI (5). The extensive necrosis seen at post mortem in case 7 was surprising. Even though the Cr VI had been taken orally 41 days previously, the colon had mucosal sloughing and necrosis throughout its length. This finding together with the universal presence of upper gastrointestinal pathology following rectal Cr VI raises the possibility of intestinal mucosal damage from blood-borne Cr VI.

In none of our cases did the plain abdominal radiographs show either a nephrogram or barium enema pattern which has been reported to occur in dichromate poisoning (personal communication Professor J.Milne).

With the incorporation of a toxic substance such as potassium dichromate in commonly used purgatives, it might be expected that larger numbers of patients should be presenting in renal failure. There are probably several explanations why this is not so. Firstly hexavalent chromium is probably detoxified to the trivalent form by organic material mixed in some of the enemas. Secondly patients are only recognised as having Cr VI poisoning if the attending medical staff have a high index of suspicion, and many cases may pass undiagnosed. Thirdly some cases of unexplained death are the result of Cr VI toxicity as demonstrated in the forensic data (page 64).

The presence of significant quantities of a digoxin-like substance in the blood of case 1 probably resulted from the incorporation of organic material in the enema. Hutchings and Terblanche (50) reported the presence of cardiac glycosides in plants of the Hyacinthaceae family. This family and others of the superorder Liliiflorae are used in Zulu and Xhosa

traditional herbal remedies. An alternative explanation may be offered by reports of a digoxin-like immunoreactive substance noted in the plasma of patients with either liver disease (51) or renal failure (52), however this would not explain the presence of a digoxin-like substance in the enema fluid itself.

ANALYSIS METHODS

Samples including blank and spiked controls were analysed by the same method, which entailed firstly, a process of extraction or digestion, followed by atomic absorption analysis.

The dry ashing technique of digestion required the measurement of 1 ml of liquid or 1 gm of tissue into a quartz crucible, which was then dried overnight in an oven at 130 deg.C. Next morning the remaining sample was ashed in a furnace at 490 deg.C, if the ashing process was not complete the sample was redissolved in concentrated nitric acid and reashed. When ashing was complete the contents of the crucible were redissolved with 1 ml of concentrated nitric acid overnight and after addition of 2,5 mls of distilled water transferred to a centrifuge tube. The crucible was repeatedly washed with distilled water, which was added to the centrifuge tube until the volume was made up to 10 ml. After centrifugation the supernatant was analysed by atomic absorption.

Atomic absorption analysis ; samples of the prepared solutions were aspirated into a reducing air-acetylene flame. The resulting absorbance was measured at a wavelength of 357,9 nm. with a slit width of 0,2 nm.. The calibration range was linear from 0 - 1,5 ppm. Samples above this range were diluted with 10% nitric acid until in range. When solutions were at the very low end of the calibration range, 200 ml samples were evaporated and redissolved to a volume of 20 ml, to bring them into mid-range. The absorbance of a blank specimen run at the same time was subtracted from the absorbance value of the specimen. Three measurements of absorbance were taken for each sample and the variation between these values was the machine error. In absolute terms this error was very small (0,01 -0,02 ppm.), however at very low concentrations such as found in dialysate samples, it may become significant. A calibration curve was defined by the use of standard concentrations of chromium. Lastly the mean sample absorbance was converted to mg/kg (ppm.) from the

calibration curve. Errors may arise from external contamination, loss of sample during digestion, machine error, and from a non-linear calibration curve. These errors were minimised by 1: careful handling and storage of samples, 2: repeating the digestion process and by comparison with the wet ashing process (boiling samples with conc. nitric acid), 3: adjusting concentration and dilution of samples to keep absorbance in the upper range of calibration curve, 4: using the near linear range of the calibration curve.

CHROMIUM : ATOMIC ABSORPTION SPECTROMETRY RESULTS

TABLE III.(p23) The chromium content of the enema fluid was very high, (6,25 mg/l) and if it was all present in the Cr VI form, as little as 100 ml would be a potentially lethal dose (23). Blood analysis failed to demonstrate any lowering of chromium level after 4 hrs of dialysis on day 2. As will be demonstrated later the greater proportion of Cr is in the red cells and thus changes in haematocrit alone will significantly affect whole blood chromium levels. It would thus be possible to apparently raise whole blood Cr levels by removal of plasma water with ultrafiltration during dialysis. The urine concentration of 5,4 mg/l on day 2 would however suggest that some dialysable chromium is present in the blood. This dialysable chromium had almost disappeared by day 18 (Urine Cr 0,03 mg/l), whilst the whole blood Cr was still significant at 1,1 mg/l.

TABLE IV.(p29) Over a 5 day period during the recovery phase of acute tubular necrosis 12 mg of chromium were excreted in the urine. This is a small proportion of the total body chromium. By day 5 the excretion was less than 1 mg/day despite a whole blood concentration of 1,9 mg/l and recovering renal function. The early diminution of urinary Cr excretion would appear to fit well with the observations of Collins et al. who showed in the dog, a rapid early fall in dialysable Cr after Cr VI exposure.

TABLE V.(p30) The conventional measurement of dialysis clearance of a substance is made by demonstrating an arterio-venous (A-V) concentration gradient in the blood supply to and from the dialyser membrane. The data in this table fails to show any significant A-V difference in Cr concentrations during this patients second, third and fourth 4 hr dialysis

treatments. To attempt to identify an A-V gradient in any of the various blood compartments, whole blood, plasma and red cells were analysed separately but no gradient was found. During these analyses the wet ashing process appeared unsatisfactory for red cell digestion. The red cell to plasma Cr content ratio was approximately 5:1 which is similar to that reported by Fristedt et al.(12).

TABLE VI.(p36) These data differ from the other preceding tables in that the dialysis values of the 2/11/89 are those of the first dialysis received by this patient. During the first hour of dialysis there was a significant drop in whole blood Cr. In this study blood samples were separated into whole blood, red cells, plasma, and plasma water represented by the ultrafiltrate of plasma. At commencement of dialysis the red cell to plasma Cr ratio was only 2:1. This lower ratio appears to be due to an unusually high plasma Cr, which in turn is the result of a very high plasma water Cr. It is this form of Cr that has been postulated to be dialysable (33). The decline of plasma water Cr content during the dialysis was paralleled by the appearance of Cr in the dialysate. A dialysate concentration of 0,1 mg/l represents a clearance of about 3,0 mg of Cr/hr. A similar trend but to a lesser degree is seen during the second dialysis. At the end of dialysis on day 2 the dialysable Cr was 0,3 mg/l, near the limits of detection by the methods used in these studies. Total urinary excretion of Cr is a function of the dialysable concentration in blood together with the glomerular filtration rate. The increase of Cr excretion from 2,8 mg on the 6/11/89 to 9,4 mg on the 12/11/89 does not follow the pattern shown by case 3 (Table IV). As there was very little dialysable blood Cr present after the second dialysis and this patient was still dialysis dependent it would seem that the dialysable Cr may have subsequently risen. One possible hypothesis could be that due to red cell destruction intracellular Cr III was being released and subsequently excreted or

that some other body compartment was releasing Cr. This patient did drop his haemoglobin from 13,2 gm/dl to 7,3 gm/l requiring transfusion of 4 units of packed cells. Another interesting hypothesis could be that the citrate in the transfusions acted as a chelating agent by solubilising tissue bound Cr and allowing its excretion.

TABLE VII.(p44) Again the red cell to plasma Cr ratio was shown in this patient to be approximately 5:1 and the urinary Cr was significant on admission at 2,0 mg/l. The serum Cr concentration remained almost constant over a period of 20 days, despite repeated dialysis and multiple red cell and plasma transfusions. This would suggest a mobilisation of the tissue bound Cr into the blood and binding to the plasma proteins. Transferrin can bind Cr more readily than other plasma proteins and this binding is blocked in the presence of iron (34). If this patients microcytosis represents an iron deficient state it would be interesting to postulate that the increased unbound transferrin may allow more rapid mobilisation from the tissues. The post mortem tissue analysis confirms the preferential uptake of Cr by hepatocytes and renal cells.

FORENSIC DATA.

These four post mortem cases were referred to the Forensic Chemical Laboratory of the Department of Health and Population Development, Cape Town for toxicological screening, between the dates of August 1988 to December 1989. Each was a case of unexplained death, which after screening appears to have been the result of Cr VI intoxication. Two cases originated from Transkei, one from Ciskei and one from the E. Cape. *Case 3 was accompanied by a sample of black medicinal powder thought to have been ingested prior to death. On analysis this contained an extremely high concentration of Cr Results of Cr analysis are expressed as tissue Cr concentration and also as total organ Cr content. Concentrations are in ppm or mg/kg and total content in mgs.

TABLE VIII

FORENSIC DATA.

TISSUE	Cr CONC.	TOTAL Cr
CASE 1.		
Kidney	5,6 mg/kg	2,8 mg
Liver	16,5 mg/kg	24 mg
CASE 2.		
Kidney	107 mg/kg	78 mg
Liver	61 mg/kg	87 mg
Stomach	- - - -	55 mg
CASE 3.*		
Kidney	195 mg/kg	- - -
Liver	530 mg/kg	- - -
Stomach	170 mg/kg	- - -
CASE 4.		
Kidney	73 mg/kg	- - -
Liver	75 mg/kg	- - -
Gall Bladder	53 mg/kg	- - -
Stomach	28 mg/kg	- - -
Duodenum	14 mg/kg	- - -
Blood	23 mg/l	- - -

FORENSIC DATA DISCUSSION.

Table VIII shows the results of tissue chromium analysis of four post mortems carried out on cases of unexplained death. In cases where a toxin is suspected, a toxicology screen is performed which includes analysis for drugs, pesticides and metals. The tissue levels of Cr are so high that they could only be consistent with Cr VI ingestion. The macroscopic organ findings in case 2 were unremarkable except for the observation that the bowel mucosa appeared a little injected. This data is interesting in several ways, firstly as these cases came from different areas it would appear that the use of Cr VI is widespread. Secondly the concentrations in the upper bowel in cases 2, 3, and 4 are suggestive of recent oral ingestion. Thirdly the ratio of Cr content between liver and kidney tissue is variable. In Case 1 the liver to kidney Cr concentration ratio was 3 to 1 but in case 2 the ratio was 0,6 to 1, demonstrating the variable uptake by these two organs. This may be explicable by the hypothesis that the induction of liver enzymes can increase the hepatic uptake of Cr. Alcohol and anti-tuberculous drugs are two well recognised enzyme inducers. Lastly the values in cases 2, 3, and 4 are considerably higher than any prior published figures.

TREATMENT OF DICHROMATE POISONING.

All seven cases documented above, presented to this hospital several days after exposure to dichromate and non-specific measures to reduce absorption were not indicated. The specific treatment of acute Cr VI poisoning remains unproven being derived from animal studies together with infrequent case reports. Three main areas of therapy have been advocated : Firstly antidotes given orally to reduce Cr VI in the gut to the less soluble and considerably less toxic Cr III form (20), these have also been used topically after skin exposure to Cr VI (53). Secondly to increase Cr elimination by maintaining urine output, by dialysis or by the addition of chelating agents (12,14,17,54,55). Thirdly using cytoprotective agents to limit cellular injury (48,56). A 10% solution of ascorbic acid, a reducing agent, was an effective antidote in rats (57), and a dose of 1 gm/24hrs was used as an oral adjunct to the successful therapy of a 2 year old child (20). There has been controversy in the medical literature over the effectiveness of dialysis in the removal of body Cr. Ellis et al. (17) reported Cr clearances varying between 3 to 23 ml/min during haemodialysis commenced three hours post ingestion, while Walpole et al.(20) reported minimal chromium elimination during peritoneal dialysis instituted 5 hours post ingestion. Kaufman et al.(14) performed peritoneal dialysis on day 3 achieving an elimination of 22,4 mg of Cr in a 24 hour period, a plasma clearance of 2-3 ml/min. Fristedt et al.(12) removed 24 mg of Cr by haemodialysis on day 7. Iserson et al. (18) used both early haemodialysis and charcoal haemoperfusion in an adolescent with very high blood Cr (58 mg/l) but found no significant removal of Cr Pederson and Morch (15) showed that 8 hours of haemodialysis with 2 dialysers in series accelerated the decline in serum Cr and concluded that dialysis was superior to the renal excretion of Cr. The effective removal of Cr by dialysis depends on the physicochemical state of the Cr containing ions and the degree of plasma protein, red cell and tissue binding. It has been shown that Cr VI readily

enters the red cell (35), the hepatocyte (46) and the proximal renal tubular cells (41) where it is converted to the Cr III form which is not freely mobilised. Trivalent chromium in plasma is bound to transferrin and albumin with a biological half-life of 5-14 days which is not shortened by dialysis (32). Plasma water may contain colloidal or soluble complexes of Cr III (27). Colloidal Cr is rapidly taken up by the liver phagocytes (25). The soluble complexes formed with a variety of ligands, are readily excreted, and can cross dialysis membranes. Attention has only been paid to the quantitative excretion of Cr not to the form in which it is being excreted. The dog experiments of Collins et al. (33) suggested that all the excreted Cr was in the Cr III form and that the renal clearance of the blood dialysable Cr remained constant. None of the above clinical studies looked at dialysable Cr levels in the blood, but only at whole blood. In case 5 (Table VI) by separating the blood into red cells, plasma and plasma water, it has been shown that it is the plasma water Cr that is rapidly eliminated not the red cell or protein-bound Cr. This data is consistent with the animal experiments of Collins et al.(33) and can be put forward to explain the variable dialysis results noted above. The whole blood Cr level can not be expected to be a predictor of dialysability as its main components are red cell and protein bound Cr, both of which were shown in early Cr 51 studies (31) to have prolonged biological half-lives unaffected by dialysis. Similarly serum Cr also may be largely composed of non-dialysable protein bound Cr. The interaction between tissue Cr and plasma water Cr is complex and may be affected by the presence of chelating agents (16,17), including citrate and acetate in dialysis fluids, tissue cell turnover and possibly iron status. If Cr VI cellular damage is the result of highly reactive intermediates such as Cr IV and Cr V (46,47,48), then the elution of Cr III from cells would not be expected to affect the pathological processes of Cr VI toxicity. Early institution of dialysis is associated with an increased Cr clearance, but there is no evidence to suggest this is in the Cr VI form, more

likely it is in the Cr III form. Dialysis performed at a later stage as in our cases, is supportive rather than therapeutic. The role of chelating agents also remains controversial. Dimercaprol (B.A.L.) has been used clinically (12,17,20), however Ellis et al.(17) failed to show any benefit in animal studies. Poly-aminocarboxylic acid derivatives have been shown to be effective chelators in animals (54). An interesting development that requires clinical confirmation is the observation that N. acetylcysteine a free radical scavenger with chelating properties reduces dichromate induced renal injury in rats (57). Vitamin E an antioxidant (48) and thyroxine (56) have been shown to protect against Cr VI toxicity in animal models but this has not been confirmed clinically.

SUMMARY.

Seven cases of acute dichromate poisoning following use of toxic purgatives are presented together with four post mortem forensic analyses. Toxicology screening revealed these four previously unexplained deaths to be the result of Cr VI poisoning. Thus a significant mortality and morbidity from Cr VI has been demonstrated. Although chronic industrial exposure to Cr VI is well recognised, only sporadic reports of acute toxicity have appeared in the medical literature. The cases reported in this thesis demonstrate that the incorporation of Cr VI into "traditional remedies" and the widespread use of these remedies poses a public health risk to the black population of South Africa. Attempts to contact the purveyors of these purgatives directly, were unsuccessful. At present there is no restriction on the distribution of dichromates, but as a result of these studies, the authorities have been approached with a request to have dichromates registered as toxic substances and distributed with appropriate health safety warnings.

A review of the pathogenesis of Cr VI toxicity is presented, and is correlated with the chemistry of Cr. A hypothesis is proposed that the variability in clinical presentation is due in part, to the differing activity of intracellular reduction enzymes in organs.

The role of dialysis in Cr elimination from the body is discussed, together with the controversy in the medical literature. Dialysis data is presented which suggests that it is only the plasma water Cr which is significantly dialysable, and that the dialysable content of blood is not directly related to either serum or whole blood Cr concentration.

Because of the variable presentation of Cr VI poisoning and the denial of use of traditional medicines by some patients, a high index of suspicion for Cr VI toxicity should be maintained especially in cases of unexplained acute renal failure and even unexplained death.

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