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Mutagenic effects of certain common metal toxicants on mammalian systems

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Abstract. The use of metals for human benefit started more than 6000 years ago. Their harmful effects were noted much later, with the growing consciousness about environmental hazards. The different industrial processes and other adjuncts of industrial revolution have added considerably to the quantities of such metal occurring under natural conditions. An appreciable proportion enters into the formation of aerosols, known to be toxic to living systems. Assessment of the hazards posed by metal effluents and their mode of action are therefore gaining considerable importance as a part of environment protection.

Keywords. Mutagenesis; metal toxicity; mammalian genetics; pollutants; carcinogen.

1. Test Systems

Used to study mutachromosomic effects of metals range from micro-organisms to human systems. Bateman (1966) considered the use of mammals in tests of mutagenicity to be practical and more meaningful than other systems in the context of human hazards (Epstein and Shafner 1968). The ultimate goal of any mutagen testing programme is to be able to test the potential mutagen directly on the human genetic material for both immediate and long term effects or to extrapolate in human system from other test systems. With the advent of the techniques of tissue culture, both *in vivo and in vitro* systems have been adopted in detecting the effects of mutagens on different mammals (Hollstein *et al* 1979; Kilbey *et al* 1977).

2. Metals as pollutants

Industrial wastes contain a relatively large amount of metals, either in the original form, or in combination with other chemicals. Numerous publications are available regarding their toxicity (Browning 1969; Goyer and Mehlman 1976; Venugopal and Luckey 1978).

The first reported investigation of the toxic effects of nickel was published by Gmelin (1826). Many possible occupational dangers due to this element were recorded (Mastromatteo, 1967). Nickel carbonyl, an industrial pollutant, is one of its most toxic compounds (Sunderman and Selin, 1968). Cobalt is mainly used in making ink, fertilizer, electroplating, etc., and vanadium compounds in the manufacture of high quality of alloy steel and sulphuric acid. The latter exert considerable toxic effects on both human and animal systems (Browning 1969).

Arsenic, a common environmental toxicant, is found in soil, water and air. It may be released into the environment through different industrial processes as well (Anonymous 1973; Milham and Strong 1974), including application as pesticides and herbicides (Miles 1968; Wagner and Weswig 1973), or from geothermal sources (Axtmann 1975; Sabadell and Axtmann 1975).

Selenium compounds are now widely used in industrial products such as rectifiers, photoelectric batteries, alloys and paints. It has been labelled variously as a toxicant (Rosenfeld and Beath 1964; Harr and Muth 1972), a carcinogen (Nelson *et al* 1943; Tscherkes *et al* 1961) and an anticarcinogenic agent (Clayton and Baumann 1949; Harr *et al* 1973).

Some soils are contaminated with heavy metals through water (Holmes *et al* 1974). Other important sources of heavy metals are sewage sludge (Webber 1972; Baker and Chesnin 1976), composted refuse, flyash (Purves 1972) and other wastes (Bremuer 1974). Sewage sludge can increase the metal contents of the soil over hundred times in one year (Foy *et al* 1978).

3. Mode of action of metals on mammalian systems

The toxicity of any metal, as of any substance, solid, fluid or gaseous, depends upon a great many factors—the nature of its compounds, its way of entry into or contact with the body, or skin surface, its mode of action, its concentration in the atmosphere, presence of other modifying chemicals, and the susceptibility of the individual exposed to its effects (Browning 1969; Goyer and Mehlman 1976; Venugopal and Luckey 1978).

As table 1 shows, the mode of action differs according to the chemical used, at different levels. In some cases, the extact molecular mechanism has been detected, leading ultimately, as in the case of most chemical mutagens, to hazards in protein synthesis (Sharma and Sharma 1960; Drake and Baltz 1976). In others, the effects may involve the cell division and/or physical action on the entire tissue. The ultimate effect of prolonged treatment and very high doses is toxicity leading often to lethality.

4. Metals as carcinogens

More than 386 cases of lung cancer and 126 cases of cancer of the nasal cavities have been recognised among workmen occupationally exposed to nickel compounds (Sunderman and Mastromatteo 1975). The increased incidence of cancer of the respiratory tract among nickel refinery workers in Wales (Doll *et al* 1970), Norway (Pedersen *et al* 1973), Canada (Mastramatteo 1967; Virtue 1972), and Soviet Union (Saknyn and Shabynina 1970, 1973) suggests that particles of metallic

nickel, nickel subsulphide (Ni_3S_2), and nickel oxide (NiO) may be the principal respiratory carcinogens in nickel refineries (Sunderman and Mastromatteo 1975).

Epidermoid carcinomas of the skin and lungs, and precancerous dermal keratoses (Dobson and Pinto 1966; Ehlers 1974; Friedrich 1972; Goldman 1973; Lee and Fraumeni 1969; Minkowitz 1964; National Institute for Occupational Safety and Health 1973; Ott *et al* 1974; Yeh 1973; Zachariae 1972), have been recorded as caused by arsenic. Human cancers followed exposure to arsenic in water (Yeh 1973) and medications (Ehlers 1974; Goldman 1973), as well as among chemical (Ott *et al* 1974), and agricultural (Friedrich 1972; Zachariae 1972) workers.

There is no evidence that occupational exposures to cobalt are associated with increased risk of neoplasia. Heath *et al* (1971) and Swanson *et al* (1973) have found that wear particles from prostheses made from a cobalt chromium alloy are carcinogenic for rat muscles.

Carcinogenic action of selenium was reported by Nelson *et al* (1943), Tscherkes *et al* (1961), Volgarev and Tscherkes (1967) and its effect on the development of spontaneous tumours by Schrauzer and Ishmael (1974).

No concrete data are available on carcinogenic, mutagenic or teratogenic effects of vanadium exposure on humans or experimental animals (Stockinger 1967). Life-term studies in mice showed no greater incidence of spontaneous tumours than in controls (Kanisawa and Schroeder 1967).

5. Metals as anticarcinogen

Certain metals, notably selenium, have exhibited distinct anticarcinogenic effects. Animal experiments to demonstrate anticarcinogenic action of selenium were initially performed by Clayton and Baumann (1949). Shamberger (1970) similarly demonstrated a counteraction of selenate on the carcinogenic effect of 7, 12-dimethylbenzanthracene and of benzpyrene in croton oil and other co-carcinogenic dispersion media. These findings were confirmed by Riley (1968). Initial epidemiological studies show that the female human breast cancer mortality in the US is lower in areas in which grains and forage crops are high in selenium (Underwood 1961).

6. Metals with mutagenic effects

Current theories regarding the possible mechanisms through which chemical carcinogens may initiate neoplastic transformation have been assessed by Miller and Miller (1971). They have formulated a general scheme for the action of chemical mutagens with modifications evolved by Huebner and Todaro (1969) Ryser (1971), Weinstein *et al* (1971) and Jungmann and Schweepe (1972). In general, several mechanisms may be postulated:

6.1. *Genetic mechanisms*

(a) Direct action on existing DNA (somatic mutation) in which replication of chemically altered DNA causes heritable modifications of the DNA nucleotide sequence, leading to permanent changes in growth regulation.

Table 1. Effects of certain common metals on mammalian systems at different levels.

Chemicals	Test systems	Effects induced at different levels			References
		Molecular	Cellular	Histological	
1	2	3	4	5	6
Nickel					
In vivo					
As dust	Mice	..	..	Cancer	Campbell 1943
	Rat and rabbits	..	..	Sarcomas	Hueper 1952, 1955; Heath and Daniel 1964; Heath and Webb 1967
	Guineapigs	..	..	Anaplastic and adenosarcomas	Hueper 1958
	Rat	..	..	Sarcomas	Gilman 1962
As carbonyl	Man	..	..	Respiratory cancer	Bridge 1933; Baader 1937; Barnett 1949; Passey 1962
	Rat	Enzymes	..	Liver and lung	Sunderman 1971, 1973
		Tryptophane pyrolase	..	..	Sunderman 1967
		Hepatic cytochrome P–450	..	Liver	Sunderman 1968
		Demethylase	..	..	Sunderman and Liebman 1970
		RNA	..	Liver	Witschi 1972; Beach and Sunderman 1969, 1970
		m-RNA	..	..	Sunderman and Liebman 1970
		Microsomal protein	..	..	Sunderman 1970
		..	..	Carcinomas and sarcomas	Lan *et al* 1972
In Cr plating	Man	..	..	Respiratory cancer	Touraine and Ramband 1968
In grinding		..	..	..	Sunderman 1973

Table 1. (*Contd.*

1	2	3	4	5	6
In plating		..	..	..	Bourasset and Galland 1966
In polishing		..	..	..	Sunderman 1973
As peliets	Rat	..	..	Sarcomas	Mitchell *et al* 1960
In smelting and electrolysis	Man	..	..	Respiratory cancer	Loken 1950, 1956; Rockstroh 1958; Znamenskii 1963; Pedersen *et al* 1973
As sulphate	Rodent	..	..	Non-carcino-genic	Sunderman 1973
	Rat	DNA, RNA and protein	Chromo-some changes	Liver, kidney, lung, brain	Banerjee *et al* 1979
As sulphide	Rat and mice	..	..	Sarcomas	Gilman 1962
As nickelocene	Hamster	..	..	..	Frust and Schlauder 1971
In vitro					
As carbonyl	Rat	RNA	..	Liver	Witshi 1972; Beach and Sunderman 1969, 1970
As chloride	Rat embryo muscle cell	Glycolytic enzyme	..	..	Swierenga 1970
	Mouse L-929 cells	Protein	..	..	Tregan and Frust 1970
As dust	Horse	Amino acids	..	..	Heath and Daniel 1964; Webb and Weinzieri 1972
As sulphate	Rat embryo muscle cell	Glycolytic enzyme	..	..	Swierenga 1970
		..	Mitotic spindle	..	Swierenga and Basrur 1968
As sulphide	Rat embryo muscle cell	..	Mitotic changes	..	Basrur and Gilman 1963, 1967
		Glyceral-dehyde-3-phosphate dehydrogenase	..	..	Swierenga 1970

Table 1. (*Contd.*)

1	2	3	4	5	6
Not specified	Mouse cell line	..	Chromosome changes	..	Olinici *et al* 1973
Cobalt					
In vivo					
As chloride	Guineapig	Nucleic acids, proteins, phosphatases, cytochrome-oxidase, glucose-6-phosphatase	..	Liver pancreas, kidney	Beskid 1963, 1967
		..	..	Adrenal glands, hypophysis, pancreas	Creutzfeld and Schmidt 1954; Van Campenhout 1955; Beskid 1963
		β-Glucuronidase, DNAase and cathepsins	..	Kidney	Novikoff *et al* 1956; Novikoff 1962; DeDuve 1959, 1963; Straus 1956
	Rat	DNA, RNA, protein	Chromosome changes	Liver, kidney, lung, brain	Banerjee *et al* 1979
	Rabbit	Cholesterol	..	Liver	Boyd and MacClean 1959
	Mice	Glucose metabolism	..	..	Isom and Way 1974
	Not specified	DNA and RNA	..	..	Liquire–Milward 1951
As sulphate	Rat	..	Chromosome changes	..	Banerjee *et al* 1979
		DNA, RNA, protein	..	Liver, kidney, lung, brain	Giri *et al* 1978
		..	..	Heart	Wiberg 1968
As radio cobalt	Mouse	Amino acids	..	..	Maynard 1958
Not specified		Alkaline phosphatase	..	Kidney	Dunn 1948
In vitro					
Not specified	Mammalian cells	Tricarboxylic acid cycle	..	..	Dingle *et al* 1962; Webb 1962; Rona 1971
	Rat	Acid phosphatase	..	Kidney and liver	Levy *et al* 1950

Table 1. (*Contd*)

1	2	3	4	5	6
As chloride	Not specified	Hepatic microsomal cytochrome-P–450	..	Liver	Tephly and Hibbeln 1971
Arsenic					
In vivo					
As arsenate	Mice	..	..	Foetal anomalies	Hood and Bishop 1972
	Not specified	DNA	..	..	Grunicke *et al* 1973
	Rat	..	Mitochondria	Kidney	Fowler 1974, 1975; Brown *et al* 1976
	Rat	..	Chromosome changes	..	Giri *et al* 1979
	Rat	DNA, RNA and protein	..	Liver, kidney, lung, brain	Giri *et al* 1979
As arsenite	Not specified	DNA	..	..	Grunicke *et al* 1973
As drugs	Man	..	..	Skin cancer	Neubauer 1947
As pesticides		..	..	Death	Chisolm 1970; Deeths and Breeden 1971
As arsine gas	Man	..	..	Lethality	Fowler and Weissberg 1974
As As_2O_3		..	..	Respiratory cancer	Lee and Fraumeni 1969
		..	..	Liver and blood	Tokanehara *et al* 1956
		..	..	Milanosis	Nagai *et al* 1956
		..	..	Liver	Eiji 1955; Yamashita *et al* 1972
As inorganic arsenic		..	..	Lung cancer	Blot and Fraumeni 1975
As arsenic salts	Mice and rat	..	..	Foetus	Hood and Bishop 1972
Not specified	Man	..	..	Dermal keratosis	Tseng *et al* 1968; Yeh 1973
	Not specified	..	..	Liver and kidney	Done and Pearl 1971

Table 1. (*Contd.*)

1	2	3	4	5	6
In vitro					
As arsenate	Human dermal cell	DNA	..	..	Jung and Trachsel, 1970; Jung 1969, 1971
		..	Chromosome Changes	..	Paton and Allison 1972
		..	..	Cancer	Jung 1969
	Human foetal kidney cells	DNA	..	..	Giri *et al* 1979
	Mouse-L-cell	..	Mitotic changes	..	Tsuda 1974
	Not specified	..	Mitochondria	..	DeMaster and Mitchell 1970; Mitchell *et al* 1971
	Lymphatic cell	DNA, RNA	..	..	Sibatani 1959
Not specified	Human cell	DNA	..	..	Petres *et al* 1970
	Human leucocyte	..	Chromosome changes	..	Burgdorf *et al* 1977; Nordenson *et al* 1978
Selenium					
In vivo					
As selenium	Man	..	..	Non-carcinogenic	Federal Register 1974
		..	..	Teratogenic	Robertson 1970
	Rat	..	..	Carcinogenic	Shapiro 1972
	Rat	..	Haemoglobin, fibrinogen, prothrombin	..	Jaffe *et al* 1972
		..	..	Carcinogenic	Harr *et al* 1972
As selenate	Rat	..	..	Hepatoma	Tscherkes *et al* 1963
	Rat and dog	..	..	Diarrhoea and anorexia	Cummins and Kimura 1971
As selenite	Mice	..	..	Tumours	Schrauzer and Ishmael 1974
		..	..	Anticarcinogen	Clayton and Baumann 1949
		..	Chromosomes	..	Shamberger 1974
		..	..	Cancer	Shamberger and Willis 1971

Table 1. (*Contd.*)

1	2	3	4	5	6
	Rat	..	..	Cancer	Schroeder *et al* 1970a
		..	..	Neoplasia	Schroeder *et al* 1970b
		..	..	Anticarcino-genic	Harr *et al* 1973
		DNA, RNA protein	Chromosome changes	Liver, kidney, lung, brain	Giri *et al* 1979
In vitro					
As selenite	Human fibroblast	DNA	Chromosome changes	..	Nakamura *et al* 1976
			..	..	Lo *et al* 1978
	Kidney tissue of rabbit	..	Mitotic changes	..	Fukina and Kudryavtseva 1969
	Human leucocyte	..	Chromosome	..	Paton and Allison 1972
	Human foetal kidney	DNA	..	..	Giri *et al* 1979
	Not specified	..	Mitotic chromosome	..	Walker and Ting 1967
Vanadium					
In vivo					
As vanadium	Man	..	..	Heart	Schroeder 1966; Mountain *et al* 1953; Curran *et al* 1959
As dust	Rat	..	..	Lung	Roshchin 1963
As meta-vanadate		Coenzyme-A	..	..	Meekes *et al* 1971 Sorewark 1967
	Guineapig	..	..	Phagocytic activity	Kulieva 1971
	Dog	..	..	Kidney and spleen	Jackson 1912
As pentoxide	Man	..	..	Respiratory system	Sjoberg 1951; Faulkner-Hudson 1964
	Rat	L-ascorbic acid	..	Liver and kidney	Chakrabarty *et al* 1977
		DNA, RNA and protein	Chromosome changes	Liver, kidney, lung, brain	Giri *et al* 1979

Table 1. *(Contd.)*

1	2	3	4	5	6
As NH_4Vo_3	Man	..	..	Tongue and throat	Faulkner–Hudson 1964
As VCl_3	Rat and rabbits	DNA and RNA	..	Liver	Roschin 1967
In vitro					
As VCl_3	Rat and rabbits	DNA and RNA	..	Liver, kidney, lung, myocardium, stomach	Roschin 1967
As vanadium	Not specified	..	..	Lung	Waters *et al* 1974
Rubidium					
In vivo					
As rubidium	Rat	Not specified	..	..	Meltzer and Leibermann 1971
		..	..	Gonads	Glendening *et al* 1956
As chloride		DNA, RNA and protein	Chromosome changes	Liver, kidney, lung, brain	Giri *et al* 1979
In vitro					
As rubidium	Brain cell	Acetylcholine	..	..	Mann *et al* 1939
Cerium					
In vivo					
As cerium	Rat	Lipid metabolism	..	Liver	Synder and Kyker 1964; Synder *et al* 1959
		..	..	Parenchymal tissue	Fischler and Roeckel 1938
	Not specified	..	..	Liver	Grace *et al* 1957
As nitrate	Rat and mice	..	..	Abdomen	Bruce *et al* 1963
	Rat	DNA, RNA and protein	Chromosome changes	Liver, kidney, lung, brain	Giri *et al* 1979
As sulphate		..	..		Giri *et al* 1978

Table 1. (*Contd.*)

1	2	3	4	5	6
Molybdenum					
In vivo					
As Na_2MoO_4	Rat and mice	..	..	Gonads	Schroeder and Mitchner 1971
As MoO_3	Not specified	..	..	Respiratory tract	Fairhill *et al* 1945
As molybdate		..	..	Urinary excretion	Schroeder *et al* 1970a
	Rat and guineapig	..	..	Colic trembling	Karantassis 1924
	Rat	DNA, RNA and protein	Chromosome changes	Liver, kidney, lung, brain	Giri *et al* 1979
As Mo	Cattle	..	..	Testis	Thomas and Moss 1951

(b) Alteration of DNA polymerase which temporarily decreases the fidelity of DNA replication, causing mutations of the DNA genome.

(c) Chemical modification of RNA subsequently transcribed into DNA which becomes integrated into the host genome. This could involve viral RNA-primed DNA polymerase (reverse transcriptase)

(d) Defects in DNA repair systems (Hart *et al* 1979).

6.2 *Epigenetic mechanisms*

(a) Chemical modification of RNA or proteins (e.g , histones and nuclear acidic proteins) which regulate DNA template activity, causing expression of normally repressed portions of the DNA genome.

(b) Chemical modification of RNA or proteins causing depression of tumour viruses or oncogenes.

(c) Carcinogen-induced changes in immunological or humoral mechanisms leading to preferential proliferation of previously existing preneoplastic or neoplastic cells.

One or more of these mechanisms may also explain the toxic action of the different metallic pollutants on mammalian systems as given in Table 1.

Nickel, in addition to its carcinogenic property, acts as a mutagen. Witsch (1972) showed that intravenous injection of nickel carbonyl in rats inhibits RNA synthesis profoundly in hepatocytes, both *in vivo* and *in vitro* (Beach and Sunderman 1969, 1970). The mechanism is believed to be due to the inhibitory effect of nickel upon nucleolar RNA polymerase activity (Beach and Sunderman 1970). The inhibition of RNA synthesis results in inhibition of m-RNA dependent induction of hepatic enzyme synthesis (Sunderman and Leibman 1970).

Arsenic has the ability to substitute for phosphate in some cellular processes. Petres and Hundeiker (1968) and Petres *et al* (1970) suggested that arsenate causes chromosomal abnormalities by simply substituting for phosphate in the DNA chain. It also inhibits normal DNA repair processes. Both arsenate and arsenite decrease the extractability of DNA from tumour cells (Grunicke *et al* 1973), suggesting a possible occurrence of DNA-protein cross linkage. Jung and Trachsel (1970) observed sodium arsenate to inhibit methylthymidine uptake into human dermal cell *in vitro*, consistent with suppression of DNA synthesis. Paton and Allison (1972) recorded chromosomal aberrations in human leucocyte and dermal fibroblast culture exposed to sodium arsenite. Lo *et al* (1978) suggested that sodium selenite may fragment DNA, trigger DNA repair synthesis and induce chromosome aberrations in cultured human fibroblasts. The results presented for fibroblasts of normal individuals and DNA repair deficient patients are in agreement with those of Nakamura *et al* (1976). The increase of chromosome aberrations observed in fibroblasts exposed to a relatively short pulse of selenite is comparable to that found in leucocytes treated for 4 h (Nakamura *et al* 1976).

Liquier-Milevard (1951) observed cobalt to form permanent combinations with purine and pyrimidine bases, as well as with DNA. It also brought about distinct changes in the amount of nucleic acid, protein and mucopolysaccharides. Beskid (1967) demonstrated an inhibition of the activities of cytochrome oxidase, succinate dehydrogenase, and glucose-6-phosphatase; a notable reduction in alkaline phosphatase, and a decrease in leucine aminopeptidase and β-glucuronidase. Acid phosphatase remained unchanged. A decrease was seen in the contents of ribonucleic acid, protein and mucopolysaccharides with the simultaneous appearance of fatty substances, glycogen, and hyaline grains in the cells. Giri *et al* (1979) and Banerjee *et al* (1979) recorded considerable mutagenic effects of Co, Ni, Ce, V, Rb, Se, Mo and As on rats *in vivo*. Cytochemical changes included decrease in total DNA, RNA and protein contents in liver, kidney, lung and brain and chromosomal alterations, including stickiness, C-mitosis and chromosome breaks and gaps.

7. Relative activity of metals

Metals can be classified into three groups according to their action on genetic materials:

(i) *Very strong metals* : Tl, Cd, Cu, Ag, Cr, Co, Ni, Pt, Pd, Be, Hg and Au, Activity decreases towards right side of the series.

(ii) *Very active metals* : Zn, Al, Ca, Mn, Fe, Se, Rb, Sr, Sb, Ce, Th and U, Activity decreases towards right side of the series.

(iii) *Relatively inactive metals* : B, Na, K, Mg, V, As, Mo, Ba, Pb and Bi.

8. Interaction between different metals

Certain metals are known to have antagonistic interactions (Venugopal and Luckey 1978). Arsenic, for example, decreases the retention of selenium (Moxon and Dubois 1939; Dubois *et al* 1940) and its overall toxicity (Palmer and

Bonhorst 1957; Levander and Argett 1969). Haemolytic anaemia, induced in rats by exposure to selenium, has been reduced by administration of arsenite (Halverson *et al* 1970); Holmberg and Ferm (1969) reported that the concomitant injection of a nonteratogenic dose of sodium selenite with sodium arsenate protected against the teratogenicity of this arsenical in golden hamsters.

Iron and cobalt seem to share at least part of the same mediated transport across rat intestinal mucosa (Valberg 1971). Increased Co absorption in Fe deficiency and mutual inhibition of the absorption of Fe, Co, Mn and Zn in anaemic rats are reported (Schade *et al* 1970). The preferential attachment of the Fe-binding proteins of rat intestine occurs in the following series: Fe, Co, Ni, Mn, Zn (Forth and Rummel 1971). The Rb : K molar ingestion ratio influences rubidium toxicity in rats (Meltzer and Liebermann 1971). Subtoxic levels of Rb show toxicity when the ratio is 0·1 or greater; to a level equivalent to 10% of the dietary K, Rb substitutes for K. Beyond that level accumulated Rb disrupts the cell function by unknown mechanisms. Biliary excretion of Se is increased by As and Te. Hg and TI reduce the urinary excretion of Se. The faecal excretion of Se was decreased by Zn and Cd, and increased by Te and As. Mercury, TI, Cd and Te increased the Se levels in the liver, spleen and kidneys of rats. Se decreased the toxicity of these metals (Venugopal and Luckey 1978). Dietary cobalt decreased the retention of Se in the heart and skeletal muscle and to a lesser extent, in the liver and kidneys in rats (Gardiner and Nicol 1971). Cobalt deficiency may render sheep more susceptible to Se toxicity (Gabbedy 1970); Co is presumed to affect the absorption of Se in cats (Venugopal and Luckey 1978).

Vanadium toxicity is intensified by high dietary zinc (Molfino 1938), and alleviated by Vitamin C, Wright (1968) suggested that V and Cr compete at the membrane transport sites. Stocks (1960), in a statistical survey, demonstrated the involvement of V together with As and Zn in lung cancer.

9. Conclusion

Knowledge of the effects of the metals, exerted on mammalian systems, at molecular, cellular and histological levels is as yet incomplete. A general observation is the presence of a marked variability, which may be attributed to numerous causes. Therefore, in assessing the relative toxicity of any chemical on a mammalian system, let alone the human one, numerous parameters have to be taken into consideration. These include, in addition to dosage, mode of application and vehicle of administration, information regarding the precise mode of action of the chemical, its rate of detoxication, excretion and its interaction with foreign elements within the system and with endogenous substances. Caution must further be exercised in extrapolating such results to the human system, since even with closely related animals like the mouse and rat, significant differences in the enzymatic systems are observed. The differences in the test systems employed may account for the frequent discrepancies and ambiguity of results obtained on the toxic action of the same chemical.

References

Anonymous 1973 Increased heavy metals around Sudbury's smelters; *Water Pollu. Control* **111** 48–49

Axtmann R C 1975 Environmental impact of a geothermal power plant; *Science* **186** 795–803

Baader E W 1937 Berufskrebs *Neuere Ergebnisse auf dem Gebiete der Rrebsrankheiten, C Adam and D. Auter*, (eds) S Hirzel Verlag, Leipzig pp. 116–117

Baker D E and Chesnin L 1976 Chemical monitoring of soils for environmental quality and animal and human health; *Adv. Agron.* **27** 305

Banerjee R, Giri A K, Talukder G and Sharma A 1979 Effects of cobalt and nickel on mammalian cellular systems; *Indian J. Environ. Health* (in press)

Barnett G P 1949 *Annual Report of the Chief Inspector of Factories and Workshops for the year* 1948. H.M. Stationery Office, London p. 229

Basrur P K and Gilman J P W 1963 Behaviour of two cell strains derived from rat rhabdomyosarcomas; *J. Natl. Cancer Inst.* **30** 163–200

Basrur P K and Gilman J P W 1967 Morphologic and synthetic response of normal and tumor muscle cultures to nickel sulfide; *Cancer Res.* **27** 1168–1177

Bateman L B 1966 Testing chemicals for mutagenicity in a mammal; *Nature* (*London*) **210** 205–206

Beach D J and Sunderman F W Jr 1969 Nickel carbonyl inhibition of ^{14}C-orotic acid incorporation into rat liver RNA; *Proc. Soc. Exp. Biol. Med.* **131** 321–322

Beach D J and Sunderman F W Jr 1970 Nickel carbonyl inhibition of RNA synthesis by a chromatin-RNA polymerase complex from hepatic nuclei; *Cancer Res.* **30** 1645–1650

Beskid M 1963 The effect of administration of cobalt chloride on the pancreas in the guinea-pig; *Folia Histochem. Cytochem.* **1** 95–102

Beskid M 1967 The action of cobalt on kidneys of the guinea-pig; *Folia Histochem. Cytochem.* **5** 33–72

Blot W J and Fraumeni J F Jr 1975 Arsenical air pollution and lung cancer; *Lancet* **2** 142–144

Bourasset A and Galland G 1966 Cancer des voies respiratoires et exposition aux sels de nickel; *Arch. Malad. Prof.* **27** 227–229

Boyd G S and Maclean N 1959 Observations on the metabolic and histological effect of cobalt chloride in the rabbit, with particular reference to cobalt induced hypercholesterolaemia; *Q. J. Exp. Physiol.* **44** 394–403

Bremuer I 1974 Heavy metal toxicities; *Quant. Rev. Biophys.* **7** 75

Bridge J C 1933 *Annual report of the chief inspector of factories and workshops for the year* 1932; H. M. Stationery Office, London pp. 103–104

Brown M N, Rhyne B C, Goyer R A and Fowler B A 1976 Intracellular effects of chronic arsenic administration on renal proximal tubule cells; *J. Toxicol. Environ. Health* **1** 505–514

Browning E 1969 *Toxicity of Industrial Metals* 2nd ed (London : Butterworth and Co.)

Bruce D W, Hietbrink B E and DuBois K P 1963 The acute mammalian toxicity of rare earth nitrates and oxides; *Toxicol. Appl. Pharmacol.* **5** 750–759

Burgdorf W, Kurnvink K and Cervenka J 1977 Elevated sister chromatid exchange rate in lymphocytes of subjects treated with arsenic; *Human. Genet.* **36** 69

Campbell J A 1943 Lung tumours in mice and man; *Br. Med. J.* **1** 179–183

Chakrabarty D, Bhattacharyya A, Majumdar K and Chatterjee G C 1977 Effect of chronic vanadium pentoxide administration on L-ascorbic acid supplementation; *Int. J. Vit. Nutri. Res.* **47** 81–87

Chisolm J J Jr 1970 Poisoning due to heavy metals; *Pediatr. Clin. North Am.* **17** 591–615

Clayton C C and Baumann C A 1949 Diet and azo dye : Effect of diet during a period when the dye is not fed; *Cancer Res.* **9** 575–582

Creutzfeld W and Schmidt W 1954 Uber die wirkung von Kobaltchlorid auf den Blutzucker und die Pankreasinseln bei verschiedenen Nagetieren; *Arch. Exp. Pathol. Pharmakol.* **222** 487–512

Cummins C M and Kimura E T 1971 Safety evaluation of selenium sulfide antidandruff shampoos; *Toxicol. Appl. Pharmacol.* **20** 89–96

Curran G L, Azarnoff D L and Bolinger R E 1959 Inhibition of cholesterol synthesis from labelled acetate; *J. Clin. Invest.* **38** 1251–1255

DeDuve C 1959 Lysosomes, a new group of cytoplasmic particles. The Fifth Annual Symposium Publication of the Society of General Physiologists; 128–160

DeDuve C 1963 *The lysosome concept. CIBA Foundation Symposium, Lysosomes* (London : Churchill Ltd.) 1–35

Deeths T M and Breeden J T 1971 Poisoning in children—A statistical study of 1057 cases; *J. Pediatr.* **78** 299–305

De Master, E G and Mitchell R A 1970 The insensitivity of mitochondrial catalysed arsenate-water oxygen exchange reaction to dinitrophenol and to oligomycin; *Biochem. Biophys. Res. Commun.* **38** 199–203

Dingle J T, Heath J C, Webb M and Daniel M 1962 The biological action of cobalt and other metals; *Biochem. Biophys. Acta* **65** 34–46

Dobson R L and Pinto J S 1966 Arsenical carcinogenesis; in *Advances in biology of skin*, eds W Montagna and R L Dobson (New York : Pergamon Press) **8** 237–245

Doll R, Morgan L G and Speizer F E 1970 Cancers of the lung and nasal sinuses in nickel workers, *Brit. J. Cancer* **24** 623–632

Done A K and Pearl A J 1971 Acute toxicities of arsenical herbicides; *Clin. Toxicol.* **4** 343–355

Drake J W and Baltz R H 1976 The biochemistry of mutagenesis; *Ann. Rev. Biochem.* **45** 11–37

Dubois K P, Moxon A L and Olson O E 1940 Further studies on the effectiveness of arsenic in preventing selenium poisoning; *J. Nutr.* **19** 477–482

Dunn T B 1948 Sex differences in the alkaline phosphatase distribution in the kidney of the mouse; *Am. J. Pathol.* **24** 719–720

Ehlers G 1974 Klinische und histologische untersuchungen zur Frage arzneimittelbedingter Arsen-tumoren; *Z. Haut. Geschlechtskr.* **43** 763–774

Eiji H 1955 Infant arsenic poisoning by powdered milk; *Nihon iji Shimpo No.* 1649 **3**–12

Epstein S S and Shafner H 1968 Chemical mutagens in the human environment; *Nature (London)* **219** 385–386

Fairhill L T, Dunn R D, Sharpless N E and Prichard E A 1945 Toxicity of molybdenum; *U.S. Pub. Health Serv. Bull.* **293** 196–208

Faulkner-Hudson T G 1964 Vanadium : Toxicology and biological significance; *Elsevier Monographs on Toxic Agents*, (Amsterdam : Elsevier Publishing Co.)

Federal Register 1974 Selenium **39** 1355–1358

Fischler F and Roeckl K W 1938 Naunyn-Schmiedeberg's; *Arch. Exp. Pathol. Pharmakol.* **189** 4–12

Forth W and Rummel W 1971 Absorption of iron and chemically related metals *in vitro* and *in vivo* : Specificity of the iron binding system in the mucosa of the jejunum; in *Intestinal absorption of metal ions, trace elements and radionuclides* (eds S C Skoryna and D Waldron-Edward (Oxford : Pergamon Press)

Fowler B A 1974 The morphologic effects of mercury, cadmium, lead and arsenic on the kidney; in *Trace metals in water supplies : Occurrence, significance and control.* Proceeding Sixteenth Water Quality Conf. Champaign-Urbana : Department of Engineering, University of Illinois, Illinois, USA, pp. 65–76

Fowler B A 1975 The ultrastructural and biochemical effects of arsenate on the kidney; *Proc. XVIII Int. Congr. Occup. Health Brighton, U.K.*

Fowler B A and Weissberg J B 1974 Arsine poisoning; *N. Engl. J. Med.* **291** 1171–1174

Foy C D, Chaney R L and White M C 1978 The physiology of metal toxicity in plants, *Ann. Rev. Plant Physiol.* **29** 511

Friedrich E G Jr 1972 Vulvar carcinoma *in situ* in identical twins—an occupational hazard; *Obstet. Gynecol.* **39** 837–841

Frust A and Schlauder M C 1971 The hamster as a model for carcinogenesis; *Proc. West. Pharmacol. Soc.* **14** 68–71

Fukina A M and Kudryavtseva T P 1969 *Mikroelem Med. Zhivotnovod*, ed. M Kruming (USSR : Elm Baku) 1970 *Chem. Abstr.* **73** 129114B

Gabbedy B J 1970 Toxicity in sheep associated with the prophylactic use of selenium; *Aust. Vet. J.* **46** 223–226

Gardiner M R and Nicol H 1971 Cobalt-selenium interactions in the nutrition of rat; *Aust. J. Exp. Biol. Med. Sci.* **49** 291–296

Gilman J P W 1962 Metal carcinogenesis. II. A study on the carcinogenic activity of cobalt, copper, iron and nickel compounds; *Cancer Res.*, **22** 158–165

Giri A K, Sharma A and Talukder G 1978 Cytochemical effects of cobalt sulphate and ceric sulphate on mammalian system; *Bull. Inst. P.G. Med. Edu. Res.* **20** 145–147

Giri A K, Banerjee R, Talukder G and Sharma A 1979 Effects of some trace elements on mammalian systems; *Indian J. Exp. Biol.* (in press)

Glendening B L, Schrenk W G and Parrish D B 1956 Effect of rubidium in purified diet rats; *J. Nutr.* **60** 563–569

Gmelin C G 1826 Experiences sur l'action de la baryte, de la strontiane, du chrome, du molybdene, du tungstene, du tellure, de l'osmium, du platine, de l'iridium, du rhodium, du palladium, du nickel, du cobalt, de l'urane, du cerium, du feret, du manganese sur l'organisme animal; *Bull. Sci. Med.* **7** 110–117

Goldman A L 1973 Lung cancer in Bowen's disease; *Am. Rev. Respir. Dis.* **108** 1205–1207

Goyer R A and Mehlman M A 1976 *Toxicity of trace elements.* (Washington : Hemisphere Publishing Co.)

Grace J G, Garst E L and Lowry W E 1957 Comparative toxicity of stable rare earth compounds; *Arch. Ind. Hyg. Occup. Med.* **15** 9

Grunicke H, Bock K, Becker H, Gang V, Schnierda J and Puschendorf B 1973 Effect of alkylating antitumor agents on the binding of DNA to protein ; *Cancer Res.* **33** 1048–1053

Halverson A W, Tsay D T, Triebwasser K C and Whitehead E I 1970 Development of hemolytic anemia in rats fed selenite; *Toxicol. Appl. Pharmacol.* **17** 151–159

Harr J R and Muth O H 1972 Selenium poisoning in domestic animals and its relationship to man; *Clin. Toxicol.* **5** 175–184

Harr J R, Exon J H, Whanger P D and Weswig P H 1972 Effect of dietary selenium on N-2-fluroenyl acetamide (FAA)-induced cancer in vitamin E supplemented selenium depleted rats; *Clin. Toxicol.* **5** 187–194

Harr J R, Exon J H, Weswig P H and Whanger P D 1973 Relationship of dietary selenium concentration, chemical cancer induction and tissue concentration of selenium in rats; *Clin. Toxicol.* **6** 487–495

Hart R W, Hall K Y and Daniel F B 1979 DNA repair and mutagenesis in mammalian cells; *Proc. Symp. 5th Ann. meeting of Amer. Soc. Photobiology* (Puerto Rico: Pergamon)

Heath J C and Daniel M R 1964 The production of malignant tumors by nickel in rat; *Br. J. Cancer.* **18** 251–264

Heath J C and Webb M 1967 Content and intracellular distribution of the inducing metal in the primary rhabdomyosarcomata induced in the rat by cobalt, nickel and cadmium; *Br. J. Cancer* **21** 768–774

Heath J C, Freedman M A R and Swanson S A V 1971 Carcinogenic properties of wear particles from prostheses made in cobalt-chromium alloy; *Lancet* **1** 564–566

Hollstein M, McCann J, Angelosanto F A and Nichols W W 1979 Short-term tests for carcinogens and mutagens; *Mutat. Res.* **65** 133–226

Holmberg R E and Ferm V H 1969 Interrelationships of selenium, cadmium, and arsenic in mammalian teratogenesis; *Arch. Environ. Health* **18** 873–877

Holmes C W, Slade E A and Mclessan C J 1974 Migration and redistribution of zinc and cadmium in marine estuarine systems; *Environ. Sci. Technol.* **3** 255

Hood R and Bishop S L 1972 Teratogenic effects of sodium arsenate in mice ; *Arch. Environ. Health* **24** 62–65

Huebner R J and Todaro G J 1969 Oncogenes of RNA tumor viruses as determinants of cancer; *Proc. Nat. Acad. Sci.* **64** 1087–1091

Hueper W C 1952 Experimental studies in metal carcinogenesis. I. Nickel cancer in rats; *Tex Rep. Biol. Med.* **10** 167–186

Hueper W C 1955 Experimental studies in metal carcinogenesis. IV. Cancer produced by parentally introduced metallic nickel; *J. Nat. Cancer Inst.* **16** 55–67

Hueper W C 1958 Experimental studies in metal carcinogenesis IX. Pulmonary lesions in guinea-pigs and rats exposed to prolonged inhalation of powdered metallic nickel; *Arch. Pathol.* **65** 600–607

Isom G E and Way J L 1974 Alteration of *in vivo* glucose metabolism by cobaltous chloride; *Taxicol. App. Pharmacol.* **27** 131–139

Jackson D E 1912 The pulmonary action of vanadium together with a study of the peripheral reaction to the metal; *Pharmacol. Exp. Ther.* **4** 1–10

Jaffe W G, Mondragon M C, Layrisse M and Ojeda A A 1972 Toxicity symptoms in rats fed organic selenium; *Arch. Latin Am. Nutr.* **22** 467–474

Jung E 1969 Arsenic as an inhibitor of the enzymes concerned in cellular recovery (dark repair); *Ger. Med. Mon.* **14** 614–616

Jung E 1971 Molecular biological investigation of chronic arsenic poisoning; *Z. Haut-Geschlechtskr.* **46** 35–36

Jung E G and Trachsel B 1970 Molekularbiologische Untersuchungen zur Arsencarcinogenese; *Arch. Klin. Exp. Derm.* **237** 819–826

Jungmann R A and Schweepe J S 1972 Binding of chemical carcinogens to nuclear proteins of rat liver; *Cancer Res.* **32** 952–959

Kanisawa M and Schroeder H A 1967 Life-term studies on the effects of arsenic, germanium, tin and vanadium on spontaneous tumors in mice; *Cancer Res.* **27** 1192–1195

Karantassis T 1924 Sur la toxicite des compases du Tungstene eh du Molybdene; *Bull. Csi Pharmacol.* **31** 561–564

Kilbey B J, Legator M, Nichols W W and Ramel C 1977 (eds) *Handbook of mutagenicity test procedures* (Amsterdam: Elsevier)

Kulieva T K 1971 Effect of vanadium on leukocytic activities in guinea-pig; *Izv. Akad. Nauk. Turkm. SSR Ser. Biol. Nauk* **3** 70–71

Lan T J, Hackett R L and Sunderman F W Jr 1972 The carcinogenicity of intravenous nickel carbonyl in rats; *Cancer Res.* **32** 2253–2258

Lee A M and Fraumeni J F 1969 Arsenic and respiratory cancer in man : An occupational study; *J. Nat. Cancer Inst.* **42** 1045–1052

Levander O A and Argett L C 1969 Effect of arsenic, mercury, thallium and lead on selenium metabolism in rats; *Toxicol. Appl. Pharmacol.* **14** 308–314

Levy H, Levison V and Schade A L 1950 The effect of cobalt on the activity of certain enzymes in homogenates of rat tissue; *Arch. Biochem.* **27** 34–40

Liquier-Milward J 1951 Evidence of a complex compound of cobalt with a purine base (adenine); *Nature* **167** 1068–1069

Lo L W, Koroptanick J and Stick H F 1978 The mutagenecity or cytotoxicity of selenite, "activated" selenite and selenate for normal and DNA repair deficient human fibroblast; *Mutat. Res.* **49** 305–312

Loken A C 1950 Lungecarcinom hos nikkelanbeidere, *Tidsskr. Nor. Laegeforen.* **70** 376–378

Loken A C 1956 Personal communication cited by Goldblatt M W and Goldblatt J : *Occupational carcinogenesis : Nickel industrial medicine and hygiene* ed E R A Merewether (London : Butterworth and Co.) p. 205

Mann P J G, Tennenbaum M and Quastel H J 1939 Acetyl cholinemetabolism in C.N.S.; *Biochem. J.* **133** 822

Mastromatteo E 1967 Nickel : A review of its occupational health aspects; *J. Occup. Med.* **9** 127–136

Maynard L S 1958 The influence of sulphydryl groups and their inhibitors on the distribution of radio cobalt in the organs and intracellular organelles of the mouse; *Ann. N.Y. Acad. Sci.* **72** 229–237

Meekes M J, Landolt R R, Kessler W V and Born G S 1971 Effect of vanadium on metabolism of glucose in the rat; *J. Pharmacol. Sci.* **60** 482

Meltzer H L and Leibermann K W 1971 Chronic ingestion of rubidium without toxicity : Implications for human therapy; *Experientia* **27** 672–674

Miles J R W 1968 Arsenic residues in agricultural soils of South-Western Ontario; *J. Agric. Food. Chem.* **16** 620–622

Milham S Jr and Strong T 1974 Human arsenic exposure in relation to a copper smelter; *Environ. Res.* **7** 176–182

Miller J A and Miller E C 1971 Chemical carcinogenesis : mechanisms and approaches to its control; *J. Nat. Cancer Inst.* **47** 5–14

Minkowitz S 1964 Multiple carcinomata followng ingestion of medicinal arsenic; *Ann. Intern. Med.* **61** 296–299

Mitchell D F, Shankwalker G B and Shazer S 1960 Determining the tumorigenicity of dental materials; *J. Dent. Res.* **39** 1023–1028

Mitchell R A, Chang B F, Huang C H and DeMaster E G 1971 Inhibition of mitochondrial energy-linked functions by arsenate. Evidences for a nonhydrolytic mode of inhibitor action; *Biochemistry* **10** 2049–2053

Molfino F 1938 Contributi sperimentalle allo studio dell' intoxicazione professionale da vanadio; *Rass. Med. Ind.* **9** 362–667

Mountain J T, Delker L L and Stokinger H E 1953 Studies in vanadium toxicity; *Arch. Ind. Hyg. Occup. Med.* **8** 406–411

Moxon A L and Dubois K P 1939 The influence of arsenic and other elements on the toxicity of seleniferous grains; *J. Nutr.* **18** 447–457

Nagai H, Okuda R, Nagami H, Yagi A, Mori C and Wada H 1956 Subacute-chronic arsenic poisoning in infants—subsequent clinical observations; *Shonika Kiyo* **2** 124–132

Nakamura K, Yoshikawa K, Sayato Y, Kurata H, Tonomura M and Tonomura A 1976 Studies of selenium related compounds. V. Cytogenetic effect of reactivity with DNA; *Mutat. Res.* **40** 177–183

National Institute for occupational safety and health 1973 *Criteria for a recommended standard : Occupational exposure to inorganic arsenic* (Washington : U.S. Department of Health, Education and Welfare)

Nelson A A, Fitzhugh O G and Calvery H O 1943 Liver tumors following cirrhosis caused by selenium in rats; *Cancer Res.* **3** 230–236

Neubauer O 1947 Arsenical cancer : A review *cancer Res.* **1** 192–251

Nordenson I, Beckman G, Beckman L and Nordiström S 1978 Occupational and environmental risks in and around a smelter in northern Sweden. II. Chromosomal aberrations in workers exposed to arsenic; *Hereditas* **88** 47

Novikoff A B 1962 Lizosomy a fizjologia i patologia Komorek; *Folia Morphol* **12** 275–279

Novikoff A B, Beautay H and De Duve C 1956 Electron microscopy of lysosome-rich fractions from rat liver; *J. Biophys. Biochem. Cytol.* **2** 179–184

Olinici C D, Risca R and Todorutiu C 1973 Cytogenetic observations of nickel-induced tumors in mice; *Oncol. Radiol.* **12** 41–46

Ott M, Holder B B and Gordon H L 1974 Respiratory cancer and occupational exposure to arsenicals; *Arch. Environ. Health* **29** 250–255

Palmer I S and Bonhorst C W 1957 Modification of selenite metabolism by arsenite; *J. Agric. Food. Chem.* **12** 928–930

Passey R D 1962 Some problems of lung cancer; *Lancet* **2** 107–112

Paton G R and Alison A C 1972 Chromosome change in human cell cultures induced by metal salts; *Mutat. Res.* **16** 332–336

Pedersen E, Hogetveit A C and Cauderson A 1973 Cancer of respiratory organs among workers at a nickel refinery in Norway; *Int. J. Cancer* **12** 32–41

Petres J and Hundeiker M 1968 Chromosome pulverization induced *in vitro* in cell cultures by sodium diarsenate. *Arch. Klin. Exp. Dermatol.* **231** 366–370

Petres J, Schmid-Ullrich K and Wolf U 1970 Chromosomenaberrationen an menschlichen Lymphozytem bei chronischen Arsenschaden ; *Dtsche Med. Wochenchr.* **95** 79–82

Purves D 1972 Consequences of trace element contamination of soils; *Environ. Pollut.* **3** 17

Riley J F 1968 Mast cells, co-carcinogenesis and anticarcinogenesis in the skin of mice; *Experientia* **24** 1237

Robertson D S E 1970 Selenium—a possible teratogen; *Lancet* **1** 518–519

Rockstroh H 1958 Zur Atiologie des Bronchialkrebs in arsenverarbeitenden Nickel-hutten; *Arch. Geshneulstforsch.* **14** 151–162

Rona G 1971 Experimental aspects of cobalt cardiomyopathy; *Br. Heart J.* **33** 171–174

Rosenfeld I and Beath O A 1964 *Selenium* (New York : Academic Press)

Roshchin I V 1963 *Toxicology of the rare metals* ed. Z I Izraelson, AEC–tr–6710 (Washington : Atomic Energy Commission)

Roshchin I V 1967 Toxicology of vanadium compounds used in modern industry; *Gig. i. Sanit.* **32** 26–34

Ryser H J P 1971 Chemical carcinogenesis; *New Eng. J. Med.* **285** 721–734

Sabedell J E and Axtmann R C 1975 Heavy metal contamination from geothermal sources. *Environ. Health Perspect.* **12** 1–8

Saknyn A V and Shabynina N K 1970 Some statistical data on carcinogenous hazards for workers engaged in the production of nickel from oxidized ores; *Gig. Tr. Prof. Zabol.* **14** 10–13

Saknyn A V and Shabynina N K 1973 Epidemiology of malignant neoplasms in nickel plants; *Gig. Tr. Prof. Zabol.* **17** 25–28

Schade S G, Felsher B F, Bernier G M and Conrad M E 1970 Interrelationship of cobalt and iron absorption; *J. Lab. Clin. Med.* **75** 435–441

Schrauzer G M and Ishmael D 1974 Effects of seelnium and of arsenic on the genesis of spontaneous mammary tumours in inbred C_{3H} mice; *Am. Clin. Lab. Sci.* **4** 441–447

Schroeder H A 1966 Municipal drinking water and cardiovascular death rates; *J.A.M.A.* **195** 81

Schroeder H A, Frost D V and Balassa J J 1970a Essential trace metals in man; selenium; *J. Chron. Dis.* **23** 227–243

Schroeder H A, Balassa J J and Tipton I H 1970b Essential trace metals in man : Molybdenum; *J. Chron. Dis.* **23** 481–499

Schroeder H A and Mitchner M 1971 Toxic effects of trace elements on the reproduction of mice and rats; *Arch. Environ. Health* **23** 102–106

Shamberger R J 1970 Relationship of selenium to cancer. I. Inhibitory effect of selenium on carcinogenesis; *J. Nat. Cancer Inst.* **44** 931–936

Shamberger R J 1974 Antioxidants and cancer. III. Selenium and other antioxidants decrease carcinogen-induced chromosome linkage, in *Trace Element Metabolism in Animals* III eds W G Hoekstra, J W Suttie, H E Ganther and W Mertz (Baltimore : University Park Press) pp 593–597

Shamberger R J and Willis C E 1971 Selenium distribution and human cancer mortality; *Crit. Rev. Clin. Lab. Sci.* **2** 211–221

Shapiro J R 1972 Selenium and carcinogeneis; *Ann. N.Y. Acad. Sci.* **192** 215–219

Sharma A K and Sharma A 1960 Spontaneous and chemically induced chromosome breaks; *Int. Rev. Cytol.* **10** 101–136

Sibatani A 1959 *In vitro* incorporation of ^{32}P into nucleic acids of lymphatic cell; *Exp. Cell Res.* **17** 131

Sjoberg S G 1951 Health hazards in the production and handling of vanadium pentoxide; *Arch. Ind. Health* **3** 631

Sorewark R 1967 Vanadium in some biological specimens; *J. Nutr.* **92** 183

Stokinger H E 1967 *Industrial hygiene and toxicology* 2nd ed ; (ed.) F A Patty (New York : Interscience) **2** 1171–1182

Stocks P 1960 On the relation between atmospheric pollution in urban and rural localities and mortality from cancer, bronchitis and pneumonia with particular reference to 3, 4-benzopyrene, beryllium, molybdenum, vanadium and arsenic; *Br. J. Cancer* **14** 397–410

Straus W 1956 Concentration of acid phosphatase, ribonuclease, desoxyribonuclease, β-glucuronidase, and cathepsin in "droplets" isolated from the kidney cells of normal rats; *J. Biophys. Biochem. Cytol.* **2** 513–521

Sunderman F W Jr 1967 Nickel carbonyl inhibition of cortisone induction of hepatic tryptophan pyrrolase; *Cancer Res.* **27** 1595–1599

Sunderman F W Jr 1968 Nickel carbonyl inhibition of phenobarbital induction of hepatic cytochrome-*p*-450; *Cancer Res.* **28** 465–470

Sunderman F W Jr 1970 Effect of nickel carbonyl upon incorporation of ^{14}C-leucine into hepatic microsomal proteins; *Res. Commun. Chem. Path. Pharmacol.* **1** 161–168

Sunderman F W Jr 1971 Metal carcinogenesis in experimental animals; *Food Cosmet. Toxicol.* **9** 105–120

Sunderman F W Jr 1973 The current status of nickel carcinogenesis; *Ann. Clin. Lab. Sci.* **3** 156–180

Sunderman F W Jr and Selin C E 1968 The metabolism of nickel carbonyl; *Toxicol. Appl. Pharmacol.* **12** 207–218

Sunderman F W Jr and Leibman K C 1970 Nickel carbonyl inhibition of induction of aminopyrine demethylase activity in liver and lung; *Cancer Res.* **30** 1645–1650

Sunderman F W Jr and Mastromatteo E 1975 *Nickel carcinogenesis* : *In nickel*, eds F W Sunderman Jr, F Coulston, G L Eichorn, J A Fellows, E Mastromatteo, H T Reno and M H Samitz (Washington : National Academy of Sciences)

Swanson S A V, Freeman M A R and Heath J C 1973 Laboratory tests on total joint replacement protheses; *J. Bone Jt. Surg.* **B55** 759–773

Swierenga S H H 1970 *The role of nickel in the induction of muscle tumors*, doctoral dissertation (Ontario : University of Guelph) pp 1–61

Swierenga S H H and Basrur P K 1968 Effect of nickel on cultured rat embryo muscle cells; *Lab. Invest.* **19** 663–674

Synder F and Kyker G C 1964 Triglyceride accumulation and release in the rare earth fatty liver; *Proc. Soc. Exp. Biol. Med.* **116** 890

Synder F, Cress E A and Kyker G C 1959 Lipid responses to intravenous rare earths in rats; *J. Lipid Res.* **1** 125–131

Tephly T R and Hibbeln P 1971 The effect of cobalt chloride administration on the synthesis of hepatic microsomal cytochrome P–450; *Biochem. Biophys. Res. Commun.* **42** 489–495

Thomas J W and Moss S 1951 The effect of orally administered molybdenum on growth, spermatogenesis and testis histology of young dairy bulls; *J. Dairy Sci.* **34** 929–936

Tokanehara S, Akao S and Tagaya S 1956 Blood findings in infantile arsenic toxicosis caused by powdered milk; *Shonika Rinsho* **9** 1078–1084

Touraine R and Rambaud G 1968 Les cancer bronchique primitifs a localization double unilaterale; *J. Franc. Med. Chirug.* **22** 757–967

Tregan L and Furst A 1970 Inhibition of interferon synthesis in mammalian cell cultures after nickel treatment; *Res. Commun. Chem. Pharmacol.* **1** 395–402

Tscherkes L A, Aptekar S G and Volgarev M N 1961 Hepatic tumors induced by selenium; *Byull. Eksp. Biol. Med.* **53** 78–82

Tscherkes L A, Volgarev M N and Aptekar S G 1963 Selenium caused tumors; *Acta Un. Int. Cancer* **19** 632–633

Tseng W P, Chu A M, How S W, Fong J M, Lin C S and Yeh S 1968 Prevalence of skin cancer in an epidemic area of chronic arsenicism in Taiwan; *J. Nat. Cancer Inst.* **40** 453–463

Tsuda S 1974 Effects of 2, 4-dinitrophenol, sodium arsenate and oligomycin on mitosis of mouse L cells growing in monolayer culture. Tokushina; *J. Exp. Med.* **21** 49–59

Underwood E J 1961 *Trace elements in human and animal nutrition*, 3rd edition (New York : Academic Press)

Valberg L S 1971 Cobalt absorption, in *Intestinal absorption of metal ions, trace elements and radionucleides* eds S C Skoryna and D Waldron-Edward (Oxford : Pergamon Press) pp 257–263

Van Campenhout E 1955 The cytotoxic effect of cobalt salts on the alpha cells of the islands of langerhans; *J. Exp. Zool.* **129** 535–560

Venugopal B and Luckey T D 1978 *Metal toxicity in mammals*, (New York : Plenum press)

Volgarev M N and Tscherkes L A 1967 Further studies in tissue changes associated with sodium selenate, in Selenium in biomedicine (Connecticut : AVI Publishing Co.) pp 179–184

Virtue J A 1972 The relationship between the refining of nickel and cancer of the nasal cavity; *Can. J. Otolaryngol.* **1** 37–42

Wagner S L and Weswig P 1974 Arsenic in blood and urine of forest workers; *Arch. Environ. Health Perspect.* **12** 9–18

Walker G W R and Ting K P 1967 Effects of selenium on recombination in barley; *Can. J. Genet. Cytol.* **9** 314–320

Waters M D, Gardner D E and Coffin D L 1974 Cytotoxic effects of vanadium on rabbit alveolar macrophage *in vitro*. *Toxicol Appl. Pharmacol.* **28** 253

Webb M 1962 The biological action of cobalt and other metals. III. Chelation of cations by dihydrolipoic acid; *Biochem. Biophys. Acta* **65** 47–65

Webb M and Weinzieri S M 1972 Uptake of $^{63}Ni^{2+}$ from its complexes with proteins and other ligands by mouse dermal fibroblasts *in vitro*. *Br. J. Cancer* **26** 292–298

Webber J 1972 Effects of toxic metals in sewage on crops; *Water Pollut. Control.* **71** 404

Weinstein B, Greenberger D, Sugimura S and Fink L M Chemical carcinogenesis and RNA; *Cancer Res.* **31** 651–655

Wiberg G S 1968 The effect of cobalt ions on energy metabolism in the rat; *Can. J. Biochem.* **46** 549

Witschi H 1972 A comparative study of *in vivo* RNA and protein synthesis in rat liver and lung; *Cancer Res.* **32** 1686–1694

Wright W R 1968 *Metabolic interrelationship between vanadium and chromium*, Ph.D. Thesis, North Carolina State University, Raleigh

Yamashita N, Doi M, Nishio M, Hojo H and Tanaka M 1972 Current state of Kyoto children poisoned by arsenic tainted worinaga dry milk; *Nippon Eiseigaku Zasshi* **27** 364–399

Yeh S 1973 Skin cancer in chronic arsenicalism; *Human Pathol.* **4** 469–485

Zachariae H 1972 Arsenik og cancerrisko; *Ugeskr. Laeg.* **134** 2720–2721

Znamenskii W V 1963 Occupational bronchogenic pulmonary cancers in workers extracting, isolating and reprocessing nickel ore; *Vor. Onkol.* **9** 130–131