Role of Trace Elements in Cancer

Morton K. Schwartz

Department of Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Summary

The review considers trace elements including fluorine, copper, manganese, zinc, cobalt, chromium, selenium, molybdenum, tin, vanadium, silicon, and nickel from the standpoint of their role as either inhibitory or causative agents of cancer and also the possible use of their assay in biological fluids as diagnostic or prognostic aids in patients with cancer.

Introduction

The role of trace metals in cancer has been the subject of conjecture, and reports of different authors are often conflicting and contradictory. A major reason for these discrepancies is the difficulty in analyzing trace elements and the problems that exist in collecting specimens without contamination (82). Trace elements are required in small concentrations as essential components of biological enzyme systems or of structural portions of biologically active constituents. They constitute, in toto, less than 0.01% by weight of the total body composition and those thus far defined as essential in animal deficiency experiments include iron, iodine, fluorine, copper, manganese, zinc, cobalt, chromium, selenium, molybdenum, tin, vanadium, and possibly silicon and nickel (20). The metals (all of the above except iodine, fluorine, and selenium) play their most important role as cofactors in enzymes. Iron is an important constituent of succinate dehydrogenase as well as a part of the heme of hemoglobin, myoglobin, and the cytochromes. Zinc is involved in carbonic acid (carbonic anhydrase), and in alcohol (alcohol dehydrogenase) formation, and in proteolysis (carboxypeptidase, leucine aminopeptidase, etc.) (4). Copper is present in many enzymes involved in oxidation (tyrosinase, ceruloplasmin, amine oxidase, cytochrome oxidase), and manganese is a part of enzymes involved in urea formation, pyruvate metabolism, and the galactotransferase of connective tissue biosynthesis. In addition to its role in vitamin B₁₂, cobalt is also a cofactor of enzymes involved in DNA biosynthesis and amino acid metabolism. Molybdenum plays an important role in purine metabolism; selenium is related to glutathione peroxidase, an enzyme involved in the protection of hemoglobin against injurious effects of hydrogen peroxide; and vanadium blocks cholesterol biosynthesis.

In animal deficiency studies it has been determined that selenium can prevent muscular dystrophy and liver necrosis in rats and white muscle disease in cattle. Chromium is needed for growth of rats and its deficiency leads to a reduced life-span, corneal lesions, and interference with insulin action producing a diabetic state with removal of glucose from the blood at a rate that is one-half that of animals on a chromium-containing diet. In other animal deprivation studies the growth of rats was only two-thirds that of control animals if the diet contained less than 1 to 2 ppm of tin or less than 0.1 ppm of vanadium. Fluoride is essential for growth of rats, silicon is needed for the development of skeleton and feathers of young chicks, and nickel is essential for the growth of wing and tail feathers (20).

The effects of trace elements are related to concentration and recorded observations range from a deficiency state, to function as biologically essential components, to an unbalance when excess of one element interferes with the function of another, to pharmacologically active concentrations (i.e., zinc in healing), and finally to toxic and even life-threatening concentrations (85). The purpose of this review is to consider the trace elements from the standpoint of both their role in carcinogenesis and the possible use of their assay in biological fluids as diagnostic or prognostic aids in patients with cancer. Iron and iodide will not be considered since they have been the subject of many reviews and, although present in relatively small concentrations, they are psychologically, if not physiologically, not "trace elements." The review will not consider such elements as arsenic or mercury that have been shown to be carcinogenic, but are not essential for animal growth (21, 51, 89).

Zinc

Reports of zinc values in biological fluids of cancer patients have been variable. Serum yields higher zinc levels than does plasma, presumably due to platelet breakdown. There is a diurnal variation in serum zinc concentrations, and zinc values less than the fasting concentrations are observed for 2 to 3 hr after the ingestion of food. In addition there is a decline in zinc levels with increasing age and women demonstrate lower levels than men (5). Normal RBC contain about 10 times the concentration of zinc seen in serum, and about 30% of serum zinc is bound to albumin. Zinc is presumably transported bound to a specific α₁-glycoprotein (22). Because of the possible variables in serum

---

1 Presented at the conference on Nutrition in the Causation of Cancer, May 19 to 22, 1975, Key Biscayne, Fla. This review was supported in part by USPHS Grant CA 08748 from the National Cancer Institute.
zinc levels, it has been suggested that RBC zinc concentrations may be a better indicator of zinc deficiency states. Low serum zinc levels have been observed in serum of patients with cancer of the bronchus and colon, but not in other forms of cancer (9), and in RBC, leukocytes, and granulocytes of such patients (37, 76, 86). "Hypozincemia" is a nonspecific observation and decreased serum zinc levels have been found in cirrhosis, hepatitis (88), lung infections including tuberculosis, myocardial infarction, renal insufficiency, diseases producing increased muscle metabolism, acute tissue injury (41, 82), and pregnant women (61). Steroid therapy, including administration of p.o. contraceptives, also produces a hypozincemia (18, 19).

Patients with cancer excrete as much as 3 times more zinc in their urine than do normal persons and in such patients the molybdenum excretion is decreased. Pfiestitial (56) suggested that a ratio of urinary zinc to molybdenum of > 300 is indicative of advanced cancer. Zinc levels are lower in prostatic cancer tissue than in normal prostate tissue, but they are increased in benign prostatic hypertrophy tissue (23). Liver, kidney, or lung harboring metastasis has a higher zinc content than does the corresponding normal tissue or the tumor itself (34, 90). The liver of patients with acute viral hepatitis contains less zinc than does normal liver and is accompanied by increased zinc in the urine but normal levels in serum.

Kew and Mallet (36) reported that in normal liver tissue the zinc concentration is about 78 ± 41 µg/g, wet weight; that of noncirrhotic liver tissue from patients with primary liver cancer is about 75 ± 31 µg/g; cirrhotic liver tissue from these patients is about 45 ± 23 µg/g, and the primary liver cancer itself is about 18 ± 7 µg/g. Low zinc levels have been reported in hepatic metastases from a variety of sources with greater than normal values in the liver harboring the cancer. Olson et al. (54) reported increased liver zinc concentrations in patients with cancer, and McBean et al. (43) found increased liver and kidney zinc in patients with bronchogenic, gastric, and nasopharyngeal cancer. Liver zinc concentrations of patients dying from noncancerous disease have been reported to be similar to that of individuals dying in accidents (43).

It has been reported that cancerous lung and breast tissue have a higher zinc concentration than does normal tissue (49). In 1 study the mean zinc concentration of breast cancer tissue was 5.7 times that of normal breast tissue. The values in various patients were extremely variable (66). For example in one patient the tumor had 490 µg/g of tissue and normal tissue 240 µg/g, whereas in a specimen from another patient the zinc concentration was 2.2 µg/g in the normal tissue and 1.8 µg/g in the tumor. An increased uptake of 65Zn has been found in mammary tumors of mice (84). In bones from normal individuals (human tibia) and in osteogenic sarcoma tissue, a significant difference in zinc concentration was observed (33). In 40 control specimens the value was 147.1 ± 49.8 µg/g, dry weight, compared to 465.8 ± 578.6 µg/g in 8 osteogenic sarcoma specimens.

The role of zinc as a carcinogenic agent is still subject to controversy. Excessive intake p.o. has been reported to be related to cancer of the esophagus and stomach (44, 71). Poswillo and Cohen (60) found that ingestion of zinc inhibited the development of tumors. It has been reported that a dietary deficiency of zinc inhibits the growth of Walker 256 carcinosarcoma (13, 45) and Lewis lung carcinoma (12). Survival of mice with transplanted leukemia or an ascites carcinoma was also prolonged by the deficiency (12). These effects were attributed to a zinc deficiency interfering with DNA synthesis (65). Guthrie and Guthrie (22) found that injection of 0.05 ml of 4% zinc chloride into the testes of Syrian hamsters produced embryonal carcinomas (testicular teratoma) in 2 of 49 animals. Zinc metal powder injected into the trachea and pleura of rats produced reticulosarcomas in the lungs and seminomas in the testicles in 15% of the animals (17).

An important consideration for the cancer patient is the observation that there is delayed healing in patients with zinc deficiency (28) and zinc, when administered p.o. to postoperative patients, greatly accelerates healing (25, 57–59). Zinc sulfate p.o. increased the healing rate of bed sores and leg ulcers when the serum zinc concentration before treatment was 110 µg/100 ml but not in patients with greater serum levels (61). This has been attributed to the role of zinc in protein synthesis and collagen formation. Zinc, by virtue of its presence in RNA and DNA polymerase, may account for reports of its role in regeneration of rat liver (62).

The exact role of zinc is unknown. Zinc binding may be related to cancerogenesis in the sense that the metals may effect catabolic or anabolic enzymes. Chvapil (6) has proposed that zinc is an integral part of biomembranes, may control membrane integrity, and may be involved in the stability of membranes and in lipid peroxidation-related injury. Zinc has been observed to function as a mitogen inducing blastogen transformation of lymphocytes in a fashion similar to that of phytohemagglutinin. Phytohemagglutinin effects are also greater in lymphocytes harvested from rats that had been given a high zinc diet. The role of zinc in RNA and DNA polymerase, its inhibitory effects on phosphodiesterase, and its activating effect on membrane-bound adenyl cyclase, suggest a role for zinc in cancerogenesis. Zinc also has been shown to stabilize ribosomes and the DNA double helix. The zinc content of DNA and RNA, isolated from Walker 256 carcinosarcoma and sarcoma M. 1, was greater than that in these nucleic acids isolated from livers of normal rats. Andronikashvili et al. (2) found that in DNA and RNA purified from sarcomas the zinc concentration remained constant following transplantation, but the iron, antimony, chromium, cobalt, and selenium decreased. It was concluded that the zinc was a necessary part of the growth process but that the other elements were not.

**Copper**

Copper is primarily found in serum (95%) as part of the oxidative enzyme ceruloplasmin, an α2-glycoprotein with a molecular weight of about 150,000. The remainder is present in an ionic form loosely bound to albumin. The daily adult requirement is about 2 mg/day and the majority of the
Ingested copper is rapidly converted in the liver to ceruloplasmin. Cellular copper is primarily found in mitochondria, and the adult body contains about 100 to 150 mg with the highest organ concentration in liver, kidney, heart, brain, and pancreas. Only 10 to 60 μg of copper are excreted in the urine each day.

The role of copper, hypocupremia, and elevated liver copper concentrations in Wilson’s disease are well documented and the effects of copper toxicity have been clearly described. Deficiency states have been reported in malabsorption (kwashiorkor, sprue, celiac disease), marasmic infants, infants with Mentes kinky hair syndrome, and nephrotic syndrome. Elevations of serum copper have been reported in multiple sclerosis, infection, myocardial infarction, acute and chronic liver disease, and schizophrenia (74). There is a relationship between serum copper and inflammation, and in some patients, but not all, there is a direct correlation with C-reactive protein. In patients with lymphomatous diseases the role of copper has been the subject of considerable investigation (32, 48). Elevated serum copper has also been reported following administration of estrogens or thyroid and pituitary hormones and after surgery (31).

In 6000 patients serum copper was correlated to other biochemistry tests obtained on the SMA 12/60. There was no definite correlation between serum copper and other biochemical markers such as alkaline phosphatase, lactic dehydrogenase, and transaminase. It was concluded that, although serum copper elevations are not specific indicators of particular disease, they are a relatively independent parameter. In assessing serum copper in a pediatric population, it is important to keep in mind that there is a drop in copper concentrations until the adult level is reached.

In a study of 236 patients with a variety of malignant lymphomas (excluding Hodgkin’s disease), Hrgovic et al. (31) reported a significant difference in serum copper levels related to disease activity. Levels were high in patients before therapy and were lowered during successful therapy with an observation of concentrations within normal levels during remission. A recrudescence of the levels was a premonitor of clinical relapse. The extent of elevation appeared to be much greater in patients with generalized disease compared to those with localized disease. There did not appear to be any difference in the copper levels whether the disease was lymphocytic, histocytic, mixed, or undifferentiated. The serum copper patterns were similar to serum copper levels reported by these authors in 191 adult patients with Hodgkin’s disease (30). The elevations in Hodgkin’s disease were related to increases in ceruloplasmin, whereas those in liver disease were attributed to interference with the excretion of copper in the bile. In a study of 28 patients with Hodgkin’s disease, values between 71 and 131 μg/100 ml were observed in 5 patients in complete remission, and values between 172 to 426 μg/100 ml were noted in 20 patients with active disease. Two other patients with active disease exhibited normal values (69 to 133 μg/100 ml in 117 normal persons). Hypercupremia was observed in 3 of 9 patients with reticulum cell sarcoma. Serum copper has been evaluated as an index of tumor response to radiotherapy (79). In Hodgkin’s disease serum copper determinations are useful indicators of the effectiveness of chemotherapeutic regimens used in obtaining the 1st treatment response and then as an early indicator of reactivation of disease. Elevations may occur 1 to 6 months before clinical evidence of relapse has occurred (28). Similar serum copper levels have been observed in children with Hodgkin’s disease (81).

In patients with leukemia, normal values were observed in 12 pediatric patients with acute lymphocytic leukemia who were in complete remission. In 8 patients with active disease, increased percentages of bone marrow blast cells were associated with abnormal serum copper concentrations (78, 80). Similar observations were made in 265 pediatric and 89 adult patients with acute lymphatic leukemia (29). The development of tumors in mice after administration of Maloney murine rhabdomyosarcoma virus is preceded by an increase in serum copper as is the induction of reticulum cell sarcoma-like lesions in marmosets by Herpes saimiri, or the growth of Morris hepatoma after s.c. implantation in rats (46).

Serum copper has also been found elevated in other forms of cancer including bronchogenic carcinoma (77), squamous cell carcinoma of the larynx (11), cervical and other gynecological cancer (53), bladder (1) and breast cancer, (10) but not in prostate cancer. In lung cancers elevations were found in 43 of 71 patients. A highly significant correlation was reported between serum copper and the sedimentation rate. In squamous cell carcinoma of the larynx, elevations were observed in 1 study in each of 10 patients but in another study in only 10 of 67 patients. Higher copper concentrations have also been found in cancerous tissue more than in normal laryngeal tissue. In cervical cancer and in bladder cancer the elevations are related to the stage of the disease and decrease in response to treatment. All of 23 patients with breast cancer demonstrated elevated serum copper levels (299 ± 34 μg/100 ml) compared to 20 normals (108 ± 10 μg/100 ml). In breast tissue the copper concentration in normal tissue ranged from less than 30 μg/g, wet weight, to 170 and 50 to 460 μg/g in tumor tissue. In every case the concentration in the tumor tissue was greater than the homologous normal tissue (an average of 2.3 times greater). Copper concentrations in pleural fluid of patients with cancer did not seem to differ greatly from those in benign diseases. The concentrations in 63 patients with breast cancer ranged from 35 to 152 μg/100 ml; in 28 lung cancer patients, 62 to 121 μg/100 ml; in 33 lymphoma patients, 57 to 150 mg/dl; and in 62 patients with metastatic tumors, 41 to 177 mg/dl (14). The pleural fluid copper levels were related to serum copper levels and to the pleural fluid protein. An examination of normal adult tibia and osteogenic sarcoma indicated a small but significant difference in the copper levels. In the normal bone the concentration was 6.6 μg/g, dry weight, and in osteogenic sarcoma it was 8.6 μg/g, dry weight (33).

There are a few studies concerning the cancerigenic effects of copper in animals. In rats the effects of DL-ethionine in inducing hepatoma can be inhibited by the addition of 0.25% cupric acetate to the diet. The mechanism of this
Nickel

A variety of nickel compounds and salts have been shown to be carcinogenic. The carcinogenesis is inversely related to the solubility of these compounds, and the least soluble in aqueous media appear to be the most carcinogenic. Nickel carbonyl \([\text{Ni(CO)}_4]\) has been reported to be implicated in cancer of the lung and nasal sinuses in industrial workers and as a possible carcinogen in tobacco smoke (16, 75).

The parenteral administration of \([\text{Ni(CO)}_4] (0.4 \text{ mg nickel per 100 g}) \) at intervals of 2 or 4 weeks produced 19 tumors in 121 rats. The tumors included 6 undifferentiated sarcomas, 3 fibrosarcomas, 3 carcinomas, 1 hemangioendothelioma, 1 leukemia, and 5 lymphomas. Nickel carbonyl has been shown to inhibit enzyme induction of cortisone-induced tryptophan pyrrolase and phenothiazine-induced benzopyrene hydroxylase, as well as protein synthesis and RNA synthesis, by means of interference with DNA-dependent RNA polymerase (38).

Benzopyrene induction of benzopyrene hydroxylase in rat lung is associated with an increase in the copper and manganese content of the microsomal fraction of the cell, and a decrease in the nickel and chromium content of this fraction (47). Phenobarbital also produces a nonspecific increase in microsomal copper, manganese, and zinc. It was postulated that an early event in microsomal enzyme induction may be a redistribution of endogenous activity or inhibitory metals. Administration of DDT is associated with enzyme induction and an increase in hepatic copper (47).

Beryllium

In 1973 it was reported at a National Symposium on the Current Status of Beryllium as an Occupational Hazard that the rate of mortality from lung cancer in beryllium plant employees who previously had had beryllium-induced respiratory disease was statistically significantly higher than in either all the plant employees or those who had not experienced beryllium-induced respiratory distress. Deaths from cancer of the liver and pancreas in these workers also seemed to be related to exposure (72).

Selenium

The toxicity of selenium has been known for many years. Undoubtedly, the reference in Marco Polo’s diary to horses whose hooves fell off after ingesting certain plants was a description of selenium poisoning (52). The ratio between the essential character of selenium and its toxic character is 1:100. Most recently, the relationship between methionine, vitamin E, and selenium as an essential nutrient has been appreciated, and glutathione peroxidase, an enzyme essential for peroxide protection, is selenium dependent (63). Liver damage due to selenium (10 ppm as \(\text{Na}_2\text{SeO}_4\)) can be prevented to some extent by addition of either DL-methionine, 0.50/g/100 ml, or DL-\(\alpha\)-tocopheryl acetate, 0.09 g/100 ml, but complete protection is gained by combination treatment with methionine, 0.025 g/100 ml, and tocopherol, 0.05 g/100 ml. Other antioxidants such as \(N',N\)-diphenyl-p-phenylenediamineethoxyquin (1,2-dihydropyridoxyl-2,2,4-trimethylquinoline) or butylhydroxytoluene also protected against the effects of selenium (40).

Near toxic levels of selenium have been reported to produce tumors in rats but other studies indicated that these concentrations of selenium created chronic toxic hepatitis that resembled hyperplasia (26, 50, 83). In the early studies, ingested selenium produced 11 liver tumors in 53 animals who survived 18 months, but the latter investigation indicated that only hyperplastic lesions were found in the livers of animals that lived more than 282 days.

Dietary selenium, presumably due to its antioxidant properties, has been found to prevent occurrence of tumors in animals fed or subjected to topically administered carcinogens. Clayton and Bauman (7) were able to inhibit butter yellow carcinogenesis in rats fed 5 ppm selenium, and Mautner et al. (42) found that selenopurines inhibited lymphomas to a much greater extent that the nonconjugated purines.

Shamberger et al. (69) found that previous application of sodium selenide, 0.0065 g/100 ml, reduced the incidence of carcinogenesis induced by topical application of 7,12-dimethylbenzanthracene and croton oil. Shamberger also reported a reduced incidence of 7,12-dimethylbenzanthracene-croton oil-induced papillomas in mice by dietary administration of 1 ppm of selenium (67). In the mice without selenium in the diet papillomas developed in 26 of 36, whereas in the animals with selenium in the diet papillomas were observed in 14 of 35 mice.

The specific role of selenium in inhibiting tumorigenesis is not known. Selenium is known to bind loosely to proteins and is taken up rapidly by rapidly growing tumors. The presence of selenium in the tumor cell may successfully compete with the carcinogen for binding places of the protein and thereby prevent carcinogenesis. Selenium has also been shown to interfere with genetic processes in barley and in Drosophila melanogaster (67). The protective role of selenium in carcinogenesis is also supported by the fact that there seem to be relationships between selenium occurrence in soil and forage crops and the death rate from cancer in the United States and Canada and between the levels of selenium in blood and the human death rate from cancer (68).

Trace Elements in Asbestos Cancerigenesis

Asbestos is the general term applied to a number of
fibrous silicates. Chrysolite and crocidolite appear to be more active in inducing mesotheliomas than is amosite. Chrysolite, crocidolite, and brucite, the magnesium hydroxide outer layer of chrysolite, are carcinogenic in rats. Asbestos carcinogens have been attributed to the physical characteristics of the fiber, contaminating trace metals, or organic materials on the fibers. The morphological role is supported by findings that glass fragments of 0.06 to 3 mm applied to pleura of rat lungs produced mesotheliomas in 12 to 18% of the animals (70).

Chromium, lead, and nickel have been found in high quantities in asbestos. In 1 sample of chrysolite, 5 mg of nickel, and 1 mg of chromium were found per g of fiber. In addition, high concentrations of zirconium, titanium, and manganese were found. Nickel is an integral portion of the fiber and additional nickel may be introduced during the milling process. It has been suggested that the fiber serves merely as a passive carrier of trace metals that are responsible for the carcinogenesis. It has also been reported that trace metals interfere with the metabolism of benzopyrene in the lung and maintain its presence in the cell for longer periods of time (8, 15, 27, 64). The inhibition of benzopyrene hydroxylase (aryl polycyclic hydroxylase) by nickel has been proposed as a mechanism for nickel carcinogenesis (73).

Microsomal copper and manganese were increased and microsomal nickel and chromium were decreased 72 hr after the intratracheal administration of benzopyrene, which produced a 6-fold increase in lung aryl hydrocarbon hydroxylase activity. Lung microsomal copper increased 4-fold over control levels with no changes in the other subcellular copper levels. There was 40% increase in microsomal manganese, but a 40% decrease in nuclear manganese. The microsomal concentrations of nickel and chromium were reduced to almost nondetectable levels. The trace metals may play a role in the regulation of microsomal enzyme activity in rat lung by altering the affinity of the substrates for cytochrome P-450 or by altering the specificity of the substrate heme protein affinity for the active site of the enzyme (47).

Manganese

Manganese is increased in serum of patients during the active phase of acute icteric viral hepatitis. The mean value in the patients is 2.32 ± 0.96 ng/ml compared to 0.57 ± 13 ng/ml in normals. The levels return toward normal in the subsiding phase of the disease. In postnecrotic cirrhosis, the serum but not the packed RBC manganese levels were also significantly elevated. There is a significant correlation of serum manganese and both bilirubin and aspartate aminotransferase in these patients. The increases were presumably due to either release of hepatic manganese during parenchymal necrosis or decreased hepatobiliary excretion (88). The liver has a relatively high concentration of manganese (1.5 ± 2 µg/g, wet weight) and manganese is primarily excreted into the bile. Manganese concentrations in normal human endometrium and in plasma are cyclic with highest concentrations found in the early proliferative phase (Cyclic Days 6 to 8) (24). Malignant breast tissue demonstrates much higher manganese concentrations than does homologous normal tissue (49). In 9 patients the normal tissue ranged from 72 to 24 µg/g, whereas the malignant tissue ranged from 10 to 55 µg/g, and in all cases the concentration of the malignant tissue was greater than the normal. Manganese was significantly higher in osteogenic sarcoma (6.6 ± 4.4 µg/g) than in normal tibia (4.6 ± 1.6 µg/g). Manganese is involved in glycosyltransferase and other enzymes including those needed for chondroitin sulfate synthesis and connective tissue metabolism (39).

Chromium

Chromium deficiency has been related to glucose metabolism and p.o. glucose causes increases in serum chromium in normal persons but not in diabetics. The normal serum concentration is about 2.5 µg/ml. A precise role for chromium in carcinogenesis has not been defined. It may play a role in association with calcium in the stabilization of nuclear nucleic acids (3).

Other Elements

There is little information available concerning the function of other essential elements in cancer. Cobalt concentrations in osteogenic sarcoma are not significantly different from those in normal bone. The level of cobalt in DNA extracted from Walker 256 and sarcoma M.1 cells is much higher than that from normal rat liver. Tin levels have been reported to be lower in some cancer tissues than in homologous normal tissues. The significance of these findings is unknown.

References

9. Davies, I. J., Musa, M., and Dormandy, T. L. Measurements of


Role of Trace Elements in Cancer

Morton K. Schwartz


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/35/11_Part_2/3481

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://cancerres.aacrjournals.org/content/35/11_Part_2/3481.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.