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The Current Status of Nickel Carcinogenesis *

F. WILLIAM SUNDERMAN, JR., MD.†

Department of Laboratory Medicine,
University of Connecticut School of Medicine,
Farmington, CT 06032

ABSTRACT

More than 327 cases of lung cancer and 115 cases of nasal cancer have been documented among workmen who were occupationally exposed to inhalation of nickel compounds. Epidemological studies in several countries have demonstrated that the prevalence of cancers of the respiratory tract among nickel refinery workers has been significantly greater than among the general population. Certain nickel compounds (Ni^0, $Ni(CO)_4$, Ni_3S_2) have been shown to be carcinogenic following administration to rodents by inhalation and/or by parenteral routes. Several biochemical alterations have been identified in experimental animals following exposures to carcinogenic nickel compounds. These alterations are similar to the changes which develop in animals following exposures to various other chemical carcinogens. Nickel carcinogenesis affords an attractive experimental model for research into the mechanisms of tumor induction. In addition to the serious carcinogenic hazards of nickel inhalation for industrial workers, nickel carcinogenesis may constitute a risk for the general population. Nickel has been detected in the gaseous phase of cigarette smoke, suggesting that nickel may be one of the carcinogenic constituents of tobacco. The presence of nickel in implanted therapeutic devices and prostheses may also represent a possible carcinogenic hazard for man.

Introduction

In 1932, a question was raised in the English House of Commons regarding an apparent propensity of workmen at the Mond Nickel Works in Clydach, Wales for the development of nasal cancer.[41, 42, 94] An investigation by the Chief Inspector of Factories led to the registry of 10 cases of cancer of the nose and paranasal sinuses.[12] By 1937, Baader[2] reported that 17 cases of nasal cancer and 19 cases of lung cancer had occurred among the Welsh nickel workers. During the ensuing years, studies in several countries substantiated the prevalence of cancers of the respiratory tract among nickel workers, and investigations in various species of experimental animals confirmed the carcinogenicity of certain

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† Requests for reprints should be addressed to the author at the University of Connecticut Health Center, P. O. Box G, Farmington, CT 06032.

TABLE I

CANCERS OF THE RESPIRATORY TRACT AMONG NICKEL WORKERS

Author	*Date*	*Country*	*Major Industrial Process*	*Previously Unreported Respiratory Cancers*	
				Lung	*Nose*
Bridge[12]	1933	Wales	Nickel carbonyl		10
Baader[3]	1937	Wales	Nickel carbonyl	19	7
Barnett[3]	1949	Wales	Nickel carbonyl	63	30
Loken[65,66]	1950,56	Norway	Smelting; electrolysis	5	
Rockstroh[87]	1958	Germany	Smelting; electrolysis	45	
Morgan[76]	1958	Wales	Nickel carbonyl	49	14
Sutherland[112]	1959	Canada	Smelting; electrolysis	19	7
Passey[83]	1962	Wales	Nickel carbonyl	16	
Znamenskii[133]	1963	USSR	Smelting	"several"	"many"
Tatarskaya[116,117]	1965,67	USSR	Electrolysis	3	6
Tsuchiya[121]	1965	Japan	Not specified	19	
Bourasset & Galland[11]	1966	France	Ni-plating		1
Mastromatteo[71]	1967	Canada	Smelting; electrolysis	16	9
Touraine & Rambaud[119]	1968	France	Ni-Cr plating	1	
Saknyn & Shabynina[89]	1970	USSR	Smelting	"many"	
Morgan[77]	1972	Wales	Nickel carbonyl	28	17
Pedersen[85a]	1973	Norway	Smelting; electrolysis	43	14
Present report	1973	USA	Ni-grinding & polishing	1	
			Totals:	>327	>115

nickel compounds. In 1968, nickel carcinogenesis was reviewed in the proceedings of a Seminar on Occupational Diseases of the Chest.[102] The goal of this paper is to bring the topic up-to-date, focusing particular attention upon the avenues whereby carcinogenic nickel compounds may gain entry into target cells, and upon the possible mechanisms whereby nickel may initiate neoplastic transformation.

Respiratory Cancers Observed in Nickel Workers

In table I are listed the cases of respiratory cancers which have been documented among workmen who were exposed to inhalation of nickel compounds. To date, more than 327 cases of lung cancer and 115 cases of nasal cancer have occurred among nickel workers in Wales, Norway, Germany, France, Russia, Japan, Canada and the United States. Some of these workmen were also exposed to other metals, including arsenic, chromium, and cobalt. However, inhalation of nickel apparently has been the major common factor in these industrial exposures, and most of the authors have inferred that some nickel compound was the principal carcinogen. Controversy has existed regarding the chemical nature of the carcinogenic nickel compound(s). Consideration as possible carcinogenic agents has been directed particularly upon respirable particles of metallic nickel, nickel sulfides, nickel oxides and upon the vapor of nickel carbonyl. Since respiratory cancers have occurred at nickel refineries and factories which performed diverse metallurgical operations (e.g., smelting, sintering, electrolytic separations and the Mond nickel carbonyl process), it is unlikely that any one nickel compound can be implicated as the sole carcinogenic factor. More probably, several nickel compounds are carcinogenic for man following chronic exposures by inhalation.

TABLE II

PREVALENCE OF RESPIRATORY CANCER AMONG NICKEL WORKERS

Author	*Date*	*Country*	*Years Studied*	*Exposure Group*	*Prevalence Ratio**	
					Lung	*Nose*
Hill[52]	1939	Wales	1929–1938	All workers	16	
Doll[21,22]	1958	Wales	1938–1956	All workers†	4.9	196
				Mond process‡	7.1	297
				Other workers	3.4	119
Sutherland[112]	1959	Canada	1930–1957	All workers	2.2	37
Tsuchiya[121]	1965	Japan	1957–1958	All workers	2.2	
Mastromatteo[71]	1967	Canada	1930–1965	All workers	2.9	96
				Cupola furnace§	4.4	197
				Other workers	1.8	21
Saknyn & Shabynina[89]	1970	USSR	1955–1967	All workers	1.8	
Doll et al[23]	1970	Wales	Before 1910‖	All workers	9.5	308
			1910–1914	All workers	10.5	870
			1915–1919	All workers	5.7	400
			1920–1924	All workers	6.3	116
			1925–1944	All workers	1.3	

* Multiple of age-specific male death rates from lung or nose cancers.

† From 1938 to 1956, 25.6 percent of all deaths among nickel workers in Glamorganshire, Wales were due to lung cancer, and 9.9% were due to nasal cancer.

‡ Men whose last employment was in the Mond nickel carbonyl process.

§ Men who worked $\geq$ 3 years in the cupola furnace.

‖ Year of first employment in the nickel refinery.

Prevalence of Respiratory Cancers in Nickel Refinery Workers

In table II, mortality data for pulmonary and nasal cancers among workers in nickel refineries are expressed as multiples of the age-specific death rates from these tumors in the male populations of Wales, Canada, Japan and Russia. These studies have demonstrated enhanced prevalence of cancers of the respiratory tract among nickel workers, relative to the prevalence in the general populations. Doll,[21,22] and Mastromatteo[71] and Pederson[85a] have observed that certain groups of nickel workers were subject to special risks of developing respiratory cancers. Among the Welsh workmen who were employed directly on the nickel carbonyl process; among the Canadian workmen who tended the cupola furnaces; and among the Norwegian workers who were engaged in roasting/smelting operations or in electrolytic refining, the incidences of cancers of the lung and nose were much higher than among their fellow workers in other sections of the refineries. Morgan[76] and Doll and coworkers[23] have reported that increased incidences of cancers of the lung and nose in Welsh nickel workers were limited to men who were first employed in the nickel industry prior to 1925. According to Morgan,[76] the reduction in the prevalence of respiratory cancers in Welsh nickel workers coincided with changes in the raw materials and refining procedures and with major improvements in industrial hygiene.

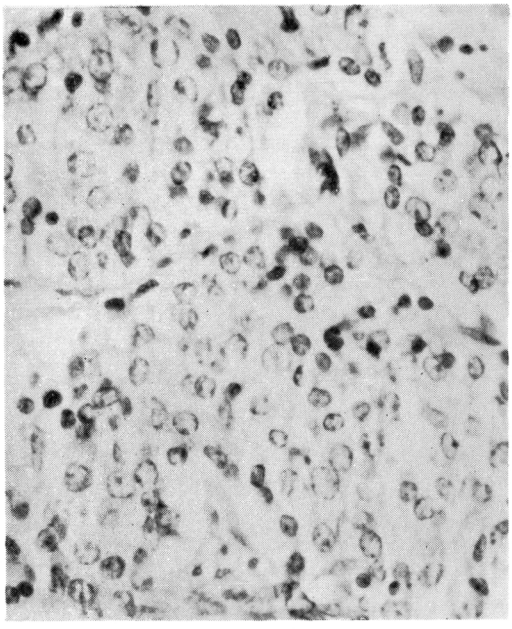

FIGURE 1. Large-cell adenocarcinoma of the lung of a nickel worker (see text). (Courtesy of E. B. Wert.) (H&E, × 250)

Respiratory Cancers in Nickel Plating and Grinding Workers

Reports by Bourasset and Galland,[11] Touraine and Rambaud,[119] and our personal observations have indicated that cancers of the respiratory tract may represent an occupational hazard among workmen who are involved in nickel plating and grinding operations. Bourasset and Galland[11] reported the occurrence of a reticulosarcoma of the nasal fossa in a 59 year old woman who had performed electrolytic nickel plating in a cutlery factory. This subject had been chronically exposed to the inhalation of vapors containing nickel and ammoniacal products of electrolysis. The latent period between first exposure and appearance of the sarcoma was five years. Touraine and Rambaud[119] reported the simultaneous occurrence of two distinct primary epidermoid carcinomas in the left lung of a 53 year old man who had been employed in an electrolytic plating shop. In addition to performing nickel-chromium plating, this man had been engaged in grinding and polishing operations and had been chronically exposed to the inhalation of dust containing both nickel and chromium. The present author has recently been consulted by Dr. Martin Perlman of Mobile, Alabama, regarding the occurrence of cancer of the lung in a 36 year old man who had been employed as a grinder and polisher of nickel-plated materials, and who had been chronically exposed to the inhalation of nickel dust. The latent period between first exposure and appearance of carcinoma was nine years. Autopsy by Dr. Earl B. Wert of Mobile, AL revealed an anaplastic large-cell adenocarcinoma in the apex of the left lung, with metastases to mediastinal lymph nodes, intestine and skin (figures 1 and 2). Nickel analyses were performed in our laboratory by atomic absorption spectrometry[81, 105] upon lung, kidney and heart tissues from this patient. In table III, these data are compared with concentrations of nickel in lung, liver and heart

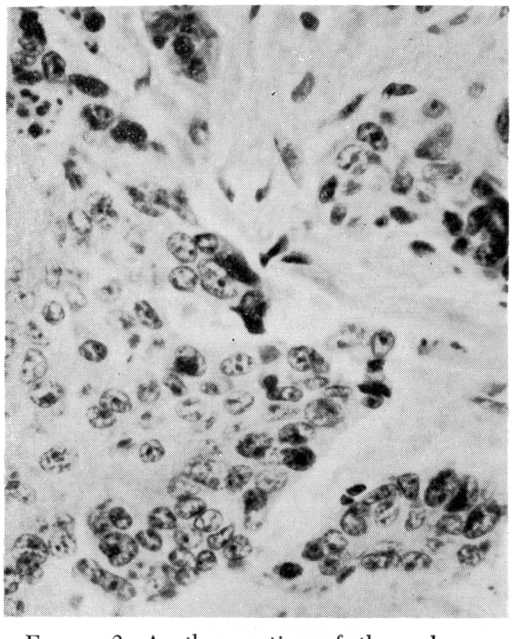

FIGURE 2. Another section of the pulmonary adenocarcinoma shown in figure 1, to illustrate the anaplastic character of the tumor. (Courtesy of E. B. Wert.) (H&E, × 250)

TABLE III

MEASUREMENTS OF NICKEL IN HUMAN TISSUES

Subject Age	*Cause of Death*	*Lung*	*Liver*	*Heart*	*Kidney*
		(*μg Ni/100 g dry wt*)			
♂ 36	Pulmonary cancer (Nickel worker)	197*	—	12	14
♂ 34	Acute $Ni(CO)_4$ poisoning	115	21	—	80
♂ 44	Stab wounds	15	2.1	2.3	—
♀ 40	Barbiturate poisoning	12	3.2	2.4	—
♂ 18	Hanging	3.3	2.6	1.6	—
♀ 22	CO poisoning	4.3	4.8	3.0	—

* Lung tissue which did *not* contain tumor.

TABLE IV

HISTOPATHOLOGY OF RESPIRATORY CANCERS IN NICKEL WORKERS

Tumor Classification	*Respiratory Cancers*	
	Lung	*Nose*
Epidermoid	34	22
Anaplastic (undifferentiated)	13	6
Alveolar cell	1	—
Adenocarcinoma	1	—
Columnar cell	—	2
Speroidal cell	—	1
Spindle cell	—	1
Scirrhus	—	1
Pleomorphic	—	15
Reticulosarcoma	—	1
Totals:	49	49

from four control subjects who were apparently in good health until they died suddenly from homicide or suicide. Also included in table III are concentrations of nickel in lung and liver of a 34 year old man who died five days after acute accidental exposure to inhalation of nickel carbonyl. As indicated in table III, the nickel burden in lung tissue of the nickel worker who had pulmonary cancer was greater than that in the patient who died of acute nickel carbonyl poisoning, and was far greater than the values which were obtained in the control subjects. This case has established a precedent in the United States for recognition of lung cancer among nickel workers as a compensable occupational disease under workmans' conpensation laws.

It may be noted that the Ministry of Pensions of Great Britain has officially designated cancer of the respiratory tract among nickel workers as a compensable occupational disease.[20]

Histopathology of Respiratory Cancers in Nickel Workers

The available data on the histopathology of cancers of the respiratory tract among nickel workers are summarized in table IV, based upon observations of Amor,[1] Perry,[86] Loken,[65, 66] Williams,[129] Morgan,[77] Bourasset and Galland,[11] Touraine and Rambaud,[119] and including the case which was described in the previous section. The nasal cancers have been reported to originate in

TABLE V

MEAN INTERVALS BETWEEN FIRST EMPLOYMENT IN NICKEL REFINERY AND DETECTION OF CANCERS

Author	*Date*	*Country*	*Years Between Entry and Diagnosis*	
			Lung Cancer	*Nose Cancer*
Barnett[3]	1948	Wales	25 (N = 72)	23 (N = 47)
Loken[65]	1950	Norway	21 (N = 3)	
Morgan[76]	1958	Wales	27 (N = 131)	23 (N = 61)
Passey[83]	1962	Wales	30 (N = 144)	
Saknyn & Shabynina[89]	1970	USSR	13 (N = ?)	

the nasal turbinates and in the ethmoid and antral sinuses. Epidermoid, anaplastic and pleomorphic carcinomas have been the most common types of respiratory cancers in the nickel workers.

Latent Periods of Respiratory Cancers in Nickel Workers

Data for the average lengths of time between first employment in a nickel refinery and occurrence of cancers of the respiratory tract are summarized in table V. Morgan's observations indicated that the average latent period for lung cancer among Welsh nickel workers was four years longer than that for nasal cancer.[76] There is wide variability in the observed latent periods for respiratory cancers in nickel workers. Thus, in Morgan's series of 131 patients with lung cancer, the intervals between first employment in the nickel refinery and occurrence of cancers ranged from less than five years to more than 40 years.[76] Similarly, in Morgan's series of 61 patients with nasal cancers, the latent periods ranged from less than 10 years to more than 40 years.[76] Saknyn and Shabynina[89] reported that Russian nickel workers who developed lung cancer had worked in the nickel refineries for an average of 13 years.

Lack of Data on Cigarette Smoking in Nickel Workers

To date, there are no available data concerning the possible relationship between cigarette smoking and occupational exposures to nickel in the induction of lung cancer. Doll and coworkers[23] have suggested that differences in the amount of cigarette smoking, which affects the incidence of lung cancer but not of nasal sinus cancers, might account for the substantial differences which they observed between age-trends for the susceptibility of nickel workers to the development of lung and nasal cancers. There is need for an epidemiological investigation of the carcinogenic interactions of cigarette smoking and occupational nickel exposures, such as have previously been reported in asbestos[92] and uranium miners.[67]

Incidence of Non-Respiratory Cancers in Nickel Workers

In contrast to the strong epidemological evidence of enhanced prevalence of cancers of the lung and nose among nickel workers, there is only scanty evidence of increased incidence of neoplasms which occur outside the respiratory tract. Doll and associates[23] found that the mortality from cancers which originated outside the respiratory tract was slightly increased among Welsh nickel workers who were employed before 1925 (49 deaths observed against 31.5 expected; $p < 0.01$). They stated that no one type of cancer accounted for this apparent excess of cancer deaths, and they attributed their observation to diagnostic confusion with cancer of the lung. In support of this view, Mastromatteo[71] did not observe any increased mortality from cancers which originated outside the respiratory tract among Canadian nickel workers. On the other hand, Saknyn and Shabynina[89] reported that the incidence of sarcomas among Russian nickel workers was 6.2 times greater than among the male urban population, and that the incidence of gastric cancer in male nickel workers, who were above the age of 50 years, was slightly but significantly greater than in the control group. Pedersen[85a] reported that 5 cases of cancer of the larynx had occurred among Norwegian nickel workers, (*vs* 1.4 expected cases), and he speculated that laryngeal cancer may be another manifestation of risk due to occupational exposure to metal.

Experimental Models of Nickel Carcinogenesis

The experimental systems which have been used to study nickel carcinogenesis in animals are summarized in table VI.

TABLE VI

EXPERIMENTAL MODELS OF NICKEL CARCINOGENESIS

Authors	*Date*	*Animals*	*Compounds*	*Route*	*Tumors*
Campbell[14]	1943	Mice	Ni dust	Inhalation	Unspecified
Hueper[54,55]	1952, 55	Rats & rabbits	Ni dust	Intravenous & intrapleural	Sarcomas
Hueper[56]	1958	Guinea pigs	Ni dust	Inhalation	Anaplastic & adenocarcinomas
Sunderman et al[95,96,97]	1959, 65	Rats	$Ni(CO)_4$	Inhalation	Epidermoid, anaplastic & adenocarcinomas
Mitchell et al[75]	1960	Rats	Ni pellets	Subcutaneous	Sarcomas
Gilman[34]	1962	Rats & mice	Ni_3S_2, NiO dusts	Intramuscular	Sarcomas
Toda[118]	1963	Rats	NiO & methylcholanthrene	Intratracheal	Epidermoid carcinomas
Heath et al[46,47]	1964, 67	Rats	Ni dust	Intramuscular	Sarcomas
Haro et al[44]	1968	Rats	Nickelocene	Intramuscular	Sarcomas
Gilman[36]	1970	Cats	Ni_3S_2 discs	Sinus implants	Epidermoid & adenocarcinomas, sarcomas
Maenza et al[68]	1971	Rats	Ni_3S_2 & 3,4-benzpyrene	Intramuscular	Sarcomas
Furst & Schlauder[33]	1971	Hamsters	Nickelocene	Intramuscular	Sarcomas
Lau et al[64]	1972	Rats	$Ni(CO)_4$	Intravenous	Carcinomas & sarcomas

TABLE VII

COMPARISONS OF VALENCES, SOLUBILITIES AND CARCINOGENICITIES OF NICKEL COMPOUNDS

Ni Compounds	*Formula*	*Solubility (mg/ml)*		*Percentage of Rats with Tumors**			
		Cold Water[123]	*Saline at 37°C*[85]	*NIH Black Rats*[84,85]	*Fischer Rats*[35]	*Fischer Rats*[31,44,61]	*Sprague-Dawley Rats*[26]
Ni(0)	Ni	Insol.	—	—	—	66	23
Ni(0) biscyclopentadiene†	$Ni\pi(C_5H_5)_2$	Insol.	—	—	—	36	—
Ni(0) tetracarbonyl	$Ni(CO)_4$	0.18	—	—	—	16	—
Ni(0)-Ni) subsulfide	Ni_3S_2	Insol.	<0.001	74	85	—	37
Ni(II) oxide	NiO	Insol.	0.003	18	10	—	—
Ni(II) monosulfide	NiS	0.004	—	—	0	—	—
Ni(II) carbonate	$NiCO_3$	0.093	0.023	40	—	—	—
Ni(II) hydroxide	$Ni(OH)_2$	0.13	—	—	75	—	—
Ni(II) fluoride	NiF_2	40	—	—	17	—	—
Ni(II) acetate	$Ni(C_2H_3O_2)_2$	—	120	7	—	22	—
Ni(II) hydrated acetate	$Ni(C_2H_3O_2)_2 \cdot 4H_2O$	—	238	5	—	—	—
Ni(II) sulfate	$NiSO_4$	293	762	0	0	—	—
Ni(II) chloride	$NiCl_2$	642	1256	0	—	—	—
Ni(III) oxide	Ni_2O_3	—	0.001	8	—	—	—
Ni(III) ammonium sulfate	$NiNH_4SO_4$	—	392	0	—	—	—

* Compounds administered i.m. or i.v. Consult original papers for dosage schedules, vehicles and durations of observation. † Nickelocene.

TABLE VIII

CARCINOGENESIS IN RATS EXPOSED TO NICKEL CARBONYL

Authors	*Date*	*Route & Schedule*	*Dosage of $Ni(CO)_4$*	*Cancer Incidence*	*Cancer Types & Locations*
Sunderman et al[95,96,97]	1959, 65	Inhalation 1 exposure	250 μg/liter/0.5 h	4% in lung*	Anaplastic & adenocarcinomas of lung
		Inhalation 150 exposures	30–60 μg/liter/0.5 h	21% in lung*	Epidermoid & adenocarcinomas of lung
Sanina[90]	1968	Inhalation 10 exposures	0.7–1.7 μg/liter/2 h	Not given	Malignancies in uterus, ovary & breast
Lau et al[54]	1972	Intravenous 1 injection	2.2 mg/100 g	8%†	Carcinoma (kidney) & sarcomas (lung & s.c. tissue)
		Intravenous 6 injections	0.9 mg/100 g	16%†	Carcinomas (liver, breast) & sarcomas (lung, liver, pancreas, uterus & s.c. tissue)

* vs 0 percent in controls. † vs 4 percent in controls.

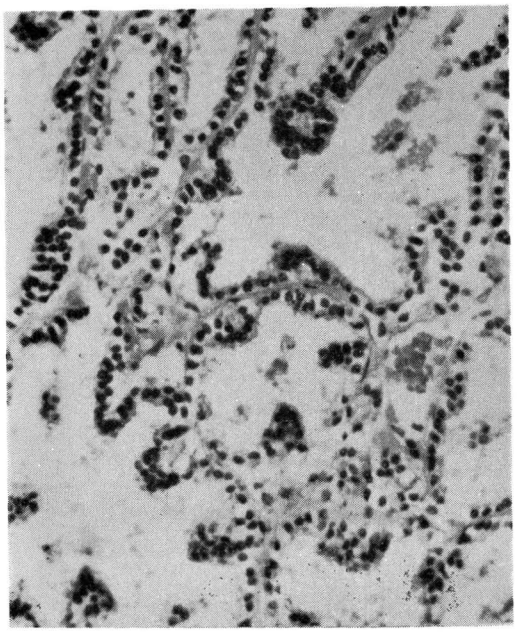

FIGURE 3. Anaplastic carcinoma in lung of a rat which had had a single exposure to inhalation of $Ni(CO)_4$. (Courtesy of F. W. Sunderman and A. J. Donnelly.) (H&E, × 250)

Huper,[54, 55] Mitchell,[75] and Heath and associates[46, 47] have found that parenteral administration of metallic nickel dust or pellets to rats, guinea pigs and rabbits results in induction of malignant sarcomas at the injection sites. Gilman[34] has shown that nickel sulfide (Ni_3S_2) is a potent inducer of rhabdomyo-sarcomas following intramuscular injection in rats. Moreover, Gilman[36] has observed epidermoid and adenocarcinomas in the sinuses of cats following implantation of nickel sulfide discs. Induction of pulmonary carcinomas in rats has been reported by Hueper[56] following inhalation of nickel dust, and by Sunderman et al[95, 96, 97] following inhalation of nickel carbonyl. Lau et al[64] have reported the occurrence of carcinomas and sarcomas in diverse organs (including liver and kidney) of rats which received multiple intravenous injections of nickel carbonyl. Toda[118] and Maenza et al[68] have found carcinogenic synergism between certain nickel compounds (NiO, Ni_3S_2) and polycyclic aromatic hydrocarbons (methylcholanthrene, 3,4-benzpyrene). On the basis of the studies which are cited in table VI, nickel carcinogenesis has been unequivocally documented in several species of animals following administration by inhalation and parenteral routes. There is no experimental evidence that nickel compounds are carcinogenic by oral or cutaneous routes of exposure.

Relative Carcinogenicity of Nickel Compounds

Fifteen nickel compounds have been tested for carcinogenicity in rats following parenteral injection. In table VII are presented comparisons of the valences, solubilities and relative carcinogenicities of these 15 compounds. The investigators who are cited in table VII used different experimental designs to test the carcinogenicity of the various nickel compounds. Payne[84, 85] and Friedmann and Bird[26] employed single i.m. implantations; Gilman[35] employed bilateral i.m. injections, and Haro et al[31, 44]

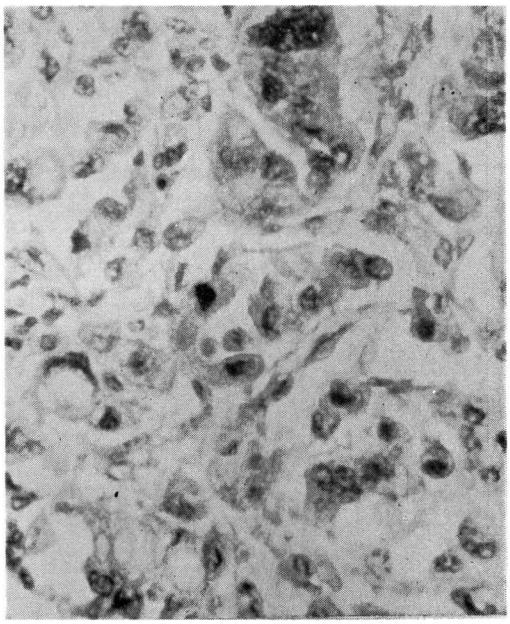

FIGURE 4. Adenocarcinoma in lung of a rat which had had a single exposure to inhalation of $Ni(CO)_4$. (Courtesy of F. W. Sunderman and A. J. Donnelly). (H&E, × 250)

and Lau et al[64] employed 5 to 12 i.m. or i.v. injections at monthly intervals. There were also significant differences among these studies in (1) the strains of rats, (2) the injection vehicles, (3) the dosage levels, (4) the durations of observation and (5) the methods of pathological examination. Hence, it is impossible to make direct comparisons of the tumor incidences which were observed in the five investigations which are cited in table VII. Nonetheless, there is a general pattern to the data. The carcinogenicities of the nickel compounds appear to be inversely correlated with their solubilities in aqueous media. Thus, the strong carcinogens, Ni_3S_2 and Ni^0, are practically insoluble in aqueous solutions, and the non-carcinogens, $NiSO_4$, $NiCl_2$ and $NiNH_4\ SO_4$, are highly soluble. There are obvious important exceptions to this rule, since NiS (which has low solubility) was not carcinogenic in Gilman's study,[35] and $Ni(C_2H_3O_2)_2$ (which is relatively soluble) was moderately carcinogenic in the studies by Payne[84, 85] and Haro et al.[44]

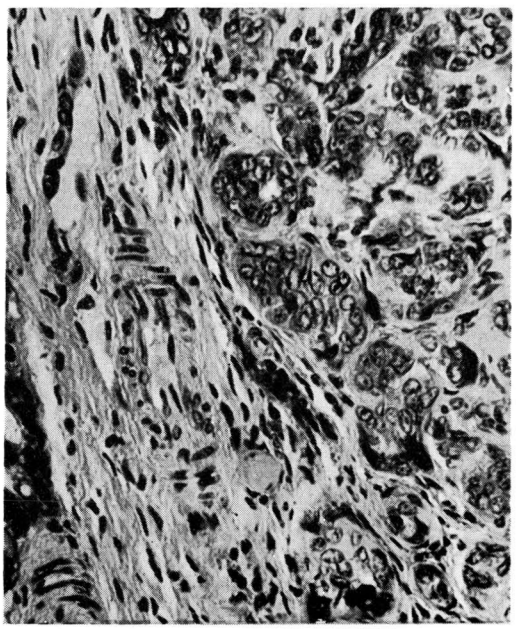

FIGURE 5. Cholangiocarcinoma of liver of a rat which received a single intravenous injection of $Ni(CO)_4$. (Lau et al.[64]) (H&E, × 250)

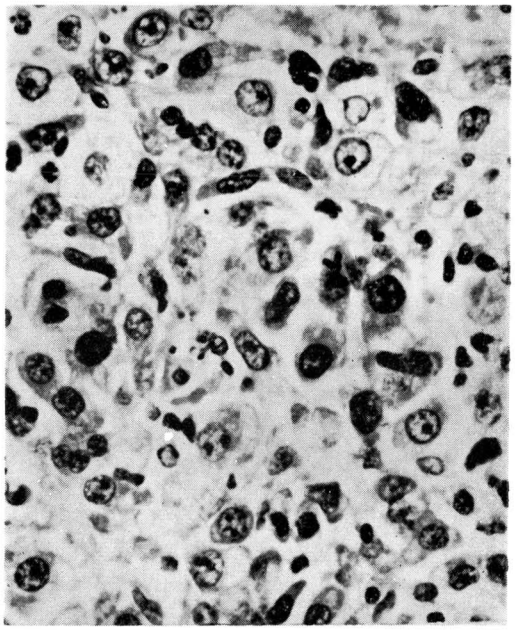

FIGURE 6. Carcinoma of kidney of a rat which received six intravenous injections of $Ni(CO)_4$. (Lau et al.[64]) (H&E, × 450)

Carcinogenesis by Nickel Carbonyl

Investigations of the carcinogenicity of nickel carbonyl, $Ni(CO)_4$, are summarized in table VIII. Particular attention has been focused upon nickel carbonyl, owing to its extreme toxicity, and its widespread uses as (1) a catalyst in the petroleum, plastics and rubber industries, (2) a vehicle for depositing thin films or coatings of nickel in the electronics industry and (3) an intermediate product in the Mond process for refining nickel matte in the nickel industry. The studies which are cited in table VIII demonstrate that cancers are induced in rats following administration of nickel carbonyl by inhalation and by parenteral injection. Lung cancers which developed in rats following inhalation of nickel carbonyl are illustrated in figures 3 and 4 and tumors of other organs which developed in rats following injections of nickel carbonyl are illustrated in figures 5 and 6. From an experimental viewpoint, the induction of lung cancers in rats by inhalation of nickel car-

TABLE IX

INDUCTION OF SARCOMAS IN RATS BY INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF Ni_3S_2

Authors	*Date*	*Strain of Rat*	*Dosage of Ni_3S_2*	*Observations*
Gilman[34]	1962	Wistar	Dust (40 mg)	Sarcoma incidence = 89% (80% rhabdomyosarcomas, 20% fibrosarcomas); lung metastases = 76%.
Gilman & Herchen[39]	1963	Fischer	Dust (20 mg) Discs (500 mg) Chips (500 mg)	No effect of physical form of Ni_3S_2 implant upon sarcoma incidence (71–95%) or lung metastases (69–100%).
Gilman & Basrur[37]	1963	Fischer	Dust (20 mg)	Precancerous changes in muscle cells: nucleolar hypertrophy; mitoses; evolution of myoblasts.
Jasmin[58,59,60]	1963–65	Fischer	Dust (10 mg)	Tumor susceptibility not sex dependent; greatest at 2 months of age; promoted by methandrostenolene.
Herchen & Gilman[50]	1964	Fischer	Discs (250 mg)	Tumorigenesis prevented by excision of Ni_3S_2 discs before 64 days after implantation.
Gilman[35]	1964	Fischer	Dust (10 mg) Discs (250 mg)	Higher sarcoma incidence after i.m. injection (80%) than after s.c. (44%) or i.p. (24%) injections. CaEDTA inhibited muscle tumorigenesis.
Kazantis & Hanbury[63]	1966	Chester-Beatty	Dust (25 mg)	Fibrosarcomas in 8 to 10 rats after s.c. injection beneath dorsal skin.
Daniel et al[18,19]	1967	3 Strains	Dust (20 mg)	Fischer and hooded rats more susceptible to Ni_3S_2 sarcomas than NIH black rats.
Corbeil[17]	1968	Fischer	Dust (10 mg)	Tumor-specific antibodies in serums from rats with Ni_3S_2 sarcomas.
Friedmann & Bird[26]	1969	Sprague-Dawley	Dust (20 mg)	Sarcona incidence = 37%: description of ultrastructure of rhabdomyosarcomas.
Hebert et al[49]	1970	Fischer	Dust (10 mg)	Arginase activity much higher in Ni_3S_2-induced rhabdomyosarcomas than in adult or embryonic muscle.
Mason[69,70]	1970	Fischer	Dust (3.3 & 10 mg)	At 3.3 mg dose, mean survival time was longer (42 wk) than at 10 mg dose (36 wk). Sarcoma incidence was not affected (97% and 85%).
Maenza et al[68]	1971	Fischer	Dust (20 mg)	Sarcoma incidence = 100% (81% rhabdomyosarcomas, 19% fibrosarcomas). Lung metastases = 57%: survival time = 33 ± 5 wk.

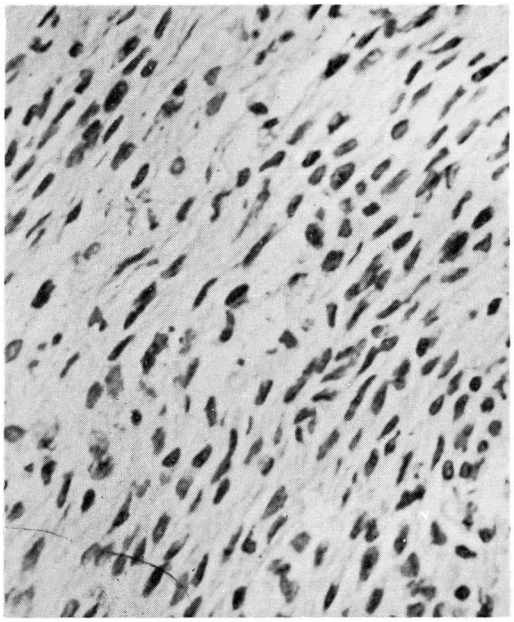

FIGURE 7. Spindle-cell fibrosarcoma in thigh of a rat at the site of a single intramuscular injection of Ni_3S_2. (Maenza et al.[68]) (H&E, × 450)

bonyl[95, 96, 97] has three principal advantages: (1) this method produces pulmonary carcinomas which closely resemble the lung cancers in nickel workers, (2) since $Ni(CO)_4$ is inhaled as a vapor, this method does not entail any problems regarding the influences of particle size upon the pulmonary retention of nickel and (3) since $Ni(CO)_4$ is rapidly absorbed by the lung and is distributed throughout the body before being metabolized and excreted in urine and expired air, $Ni(CO)_4$ is particularly suited for pharmacological studies. On the other hand, inhalation of nickel carbonyl has four practical disadvantages as a technique for studying the mechanisms of nickel carcinogenesis: (1) the latent period for induction of lung cancers is long (24 to 27 months), (2) the incidence of lung cancers is low (4 to 21 percent of two-year survivors), (3) there is necessity for specialized equipment for inhalation exposures and (4) stringent safety measures are essential in order to safeguard the investigators from accidental poisoning.

Carcinogenesis by Nickel Sulfide (Ni_3S_2)

Investigations of the induction of sarcomas in rats by intramuscular injections of nickel sulfide, Ni_3S_2, are tabulated in table IX. The carcinogenic properties of Ni_3S_2 were discovered by Gilman and Ruckerbauer[40] in 1962. They found that a powder which was collected from the dust flue of a Canadian nickel refinery was a potent carcinogen when injected intramuscularly in rats and mice. By investigating the carcinogenicity of various metallic constituents of the refinery dust (Ni_3S_2, NiO, $NiSO_4 \cdot 6H_2O$, CoS, CoO, CuS, Cu_2S, CuO, FeS, FeO, and Fe_2O_3), Gilman[34] identified Ni_3S_2 as the most carcinogenic component. Gilman[35] developed one of the simplest, most convenient and most reproducible methods of chemical carcinogenesis. Rhabdomyosarcomas and fibrosarcomas which developed in Fischer rats following injection of Ni_3S_2 are illustrated in figures 7 to 11. Induction of sarcomas in Fischer rats by intramuscular injection of Ni_3S_2 has proved to be an ex-

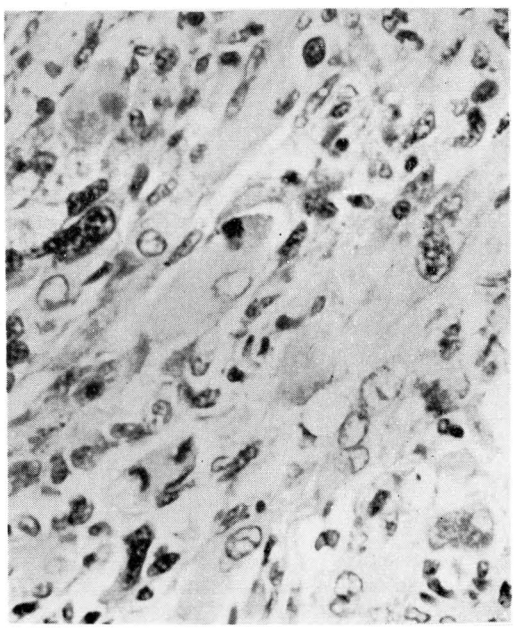

FIGURE 8. Rhabdomyosarcoma in thigh of a rat at the site of a single intramuscular injection of Ni_3S_2. (Maenza et al.[68]) (H&E, × 450)

cellent experimental system for studies of endocrine factors and cancer chemotherapy. Several cell lines which are derived from Ni_3S_2-induced sarcomas have been successfully propagated in tissue culture.[4, 5, 79, 80, 113]

Carcinogenesis by Metallic Nickel

In table X are summarized several studies of the induction of sarcomas in rats by intramuscular or subcutaneous injections of metallic nickel in the forms of pellets, dust, or sponge. According to Friedmann and Bird[26] rhabdomyosarcomas which are induced with metallic nickel are indistinguishable by biological, histological or ultrastructural criteria from the rhabdomyosarcomas which are induced with Ni_3S_2. A resume of the reported biological characteristics of the sarcomas which are induced in rats by intramuscular injections of Ni dust or Ni_3S_2 is given in table XI.

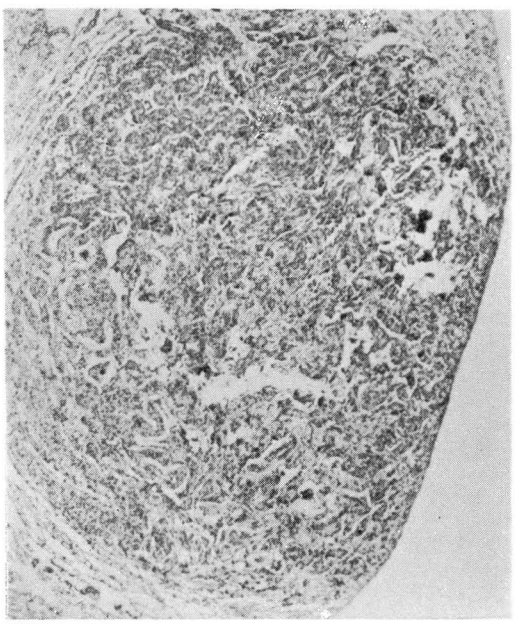

FIGURE 9. Sub-pleural pulmonary metastasis of the rhabdomyosarcoma shown in figure 8. (H&E, × 100)

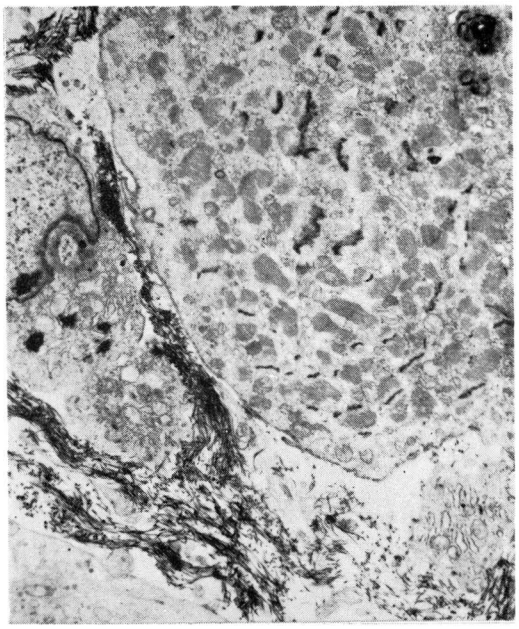

FIGURE 10. Electron micrograph of a rhabdomyoblast in the rhabdomyosarcoma shown in figure 8. The tumor cell is surrounded by fibrous collagen and fibroblasts of the supporting stroma. Note scattered myofibrils identified by dark Z-band material. (Courtesy of P. J. Goldblatt.) *Fixation:* osmium tetroxide (2 percent) buffered with s-collidine. *Staining:* uranyl acetate and lead citrate. (× 4,800)

Intracellular Transport of Nickel Compounds

Elucidating the mechanisms whereby nickel enters the target cells is an initial step in understanding nickel carcinogenesis. Three hypotheses are summarized in table XII. Gas chromatographic studies in our laboratory have shown that nickel carbonyl can cross the alveolar membrane in either direction without decomposition or metabolic alteration.[62, 108, 109] This observation has suggested that lipid-soluble, organic nickel complexes such as nickel carbonyl and nickelocene can directly penetrate cellular membranes, and thus can exert their pharmacological effects.[13, 106] It is presumed that Ni^0 is liberated intracellularly and oxidized to Ni^{2+}. According to the nickel-protein-binding hypothesis of Heath and

coworkers,[48] nickel dust and Ni_3S_2 are deposited extracellularly and are slowly oxidized to Ni^{2+}, which becomes bound to albumin and possibly other serum or tissue proteins. The nickel-protein complex, adsorbed on the myoblast surface, enters the cell by endocytosis. Hydrolysis of the proteins by lysosomal proteinases is presumed to lead to intracellular release of Ni^{2+}. The principal support for this hypothesis rests upon *in vitro* observations that nickel dust slowly dissolves in sterile horse serum and bovine albumin solutions.[48] According to the recent ultrafiltrable Ni-complex hypothesis of Weinzierl and Webb,[127] nickel becomes bound to ultrafiltrable molecules such as histidine in muscle autolysates. It is speculated that myoblasts which are involved in the repair of injured muscle actively absorb the diffusible Ni-complex(es). Experimental support for this hypothesis is based upon the findings of Weinzierl and Webb[127] that nickel dust dissolves in muscle autolysates and that 90 percent of the dissolved nickel is complexed with ultrafiltrable molecules. Moreover, Webb and Weinzierl[125] have demonstrated the cellular uptake of diffusible ^{63}Ni-complexes by mouse dermal fibroblasts in tissue culture. The three hypothetical mechanisms for the entry of nickel into target cells which are given in table XII are not mutually exclusive, and a carcinogenic nickel compound might cross cell membranes by a combination of these processes.

FIGURE 11. Higher magnification of the cytoplasm of a rhabdomyoblast from a Ni_3S_2-induced rhabdomyosarcoma. The small, irregular myofibrils are composed of bundles of thick and thin filaments, cross-striated by dark Z-band material. Irregular mitochondria and dilated vesicles of endoplasmic reticulum are also shown. (Courtesy of P. J. Goldblatt.) *Fixation and Staining:* same as figure 10. (× 31,300)

Mechanisms of Nickel Carcinogenesis

Evidence which may be related to the mechanisms of nickel carcinogenesis is summarized in table XIII. *First*, studies in our laboratory, which have recently been confirmed by Witschi,[130] have shown that intravenous injection of nickel carbonyl in rats profoundly inhibits RNA synthesis in hepatocytes, as measured *in vivo* and *in vitro*.[9, 10] The mechanism is believed to be an inhibitory effect of nickel upon nucleolar RNA-polymerase activity.[10, 107] The inhibition of synthesis of RNA results in inhibition of messenger-RNA-dependent induction of hepatic enzyme synthesis[110] (table XIV). *Second*, studies by Webb and coworkers[124] have shown that 70 to 90 percent of intracellular nickel in Ni-induced rhabdomyosarcomas is located in the nucleus, and that an average of 53 percent of nuclear nickel is present in the nucleolar fraction. Nucleolar localization of nuclear nickel has also been observed by Webb and Weinzierl[125] in mouse dermal fibroblasts grown *in vitro* in the presence of ^{63}Ni complexes. Intracellular ^{63}Ni in the fibroblasts was predominantly located within the nuclei, and one half of the nuclear ^{63}Ni was associated with the nucleolar fraction.[125] Webb and coworkers[124] emphasized the possible relationships between their find-

TABLE X

INDUCTION OF SARCOMAS IN RATS BY INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF METALLIC NICKEL

Authors	*Date*	*Strain of Rats*	*Dosage of Nickel*	*Observations*
Mitchell et al[75]	1960	Wistar	4 pellets (2 × 2 mm) s.c.	Fibrosarcoma incidence = 50%
Heath & Daniel[46]	1964	Hooded	Dust (28 mg) i.m.	Rhabdomyosarcoma incidence = 100% lymph node metastases = 30%
Heath & Webb[47]	1967	Hooded	Dust (28 mg) i.m.	Ni bound to DNA and RNA in rhabdomyosarcoma nuclei.
Friedmann & Bird[26]	1969	Sprague-Dawley	Sponge (20 mg) i.m.	Rhabdomyosarcoma incidence = 24%; tumor classification based upon differentiation of rhabdomyoblasts.
Furst & Schlauder[33]	1971	Fischer	Powder (5 mg) i.m. × 5 at 4 wk intervals	Sarcoma incidence = 76%
Webb et al[124]	1972	Hooded	Dust (28 mg) i.m.	Intranuclear Ni in rhabdomyosarcoma cells is 53% in nucleolar fraction.
Furst et al[32]	1972	Fischer	Powder (5 mg) i.m. × 6 at 4 wk intervals	Sarcomas uniformly transplantable to Fischer rats; growth of tumor transplants inhibited by chemotherapy with N-methylformamide

TABLE XI

BIOLOGICAL CHARACTERISTICS OF SARCOMAS INDUCED IN RATS BY INTRAMUSCULAR INJECTION OF Ni DUST OR Ni_3S_2

Strain Susceptibility: Fischer >Hooded >>Wistar >Sprague-Dawley >NIH Black

Dosage: 3.3 to 20 mg Ni_3S_2; 20 to 28 mg Ni dust

Latent Period: 5 to 10 months; *Survival Period:* 6 to 12 months

Maximum Susceptibility: 2 months age; *Minimum Exposure:* 2 months

Tumor Incidence: 80 to 100 percent

Tumor Histology: Rhabdomyosarcomas (80 percent), fibrosarcomas (20 percent)

Endocrine Factors: No sex difference in susceptibility; promoted by androgens; depressed by castration and hypophysectomy

Tumor Viability: May be transplanted to imbred rats and grown in tissue culture

Metastases: Lung and lymph nodes (50 to 80 percent)

Immunology: Serum contains tumor-specific antibodies

Enzymology: Arginase activity higher than in adult or embryonic muscle

Ni-binding: Ni bound to DNA, RNA and nucleoprotein, and localized particularly in rhabdomyoblast nucleoli

TABLE XII

MECHANISMS FOR INTRACELLULAR TRANSPORT OF NICKEL

I. *Lipid-Solubility Hypothesis* (Sunderman,[106] 1971). Owing to their lipid solubility, pharmacologically active nickel compounds ($Ni(CO)_4$, Nickelocene) cross cell membranes without metabolic alteration, followed by intracellular oxidation of Ni^0 to Ni^{2+}.

II. *Protein-Binding Hypothesis* (Heath et al,[48] 1969). Ni dust and Ni_3S_2 are deposited extracellularly and are slowly oxidized to Ni^{2+}, which becomes bound to proteins (e.g., serum albumin). The Ni-protein complex, adsorbed on the myoblast surface, enters the cell by endocytosis. Hydrolysis of the proteins by lysosomal proteinases leads to intracellular release of Ni^{2+}.

III. *Ultrafiltrable Ni-Complex Hypothesis* (Weinzierl and Webb,[127] 1972). The Ni^{2+} which is formed from Ni dust and Ni_3S_2 becomes bound to ultrafiltrable molecules (e.g., histidine) in muscle autolysates. Myoblasts which are involved in the repair of muscle injury actively absorb the diffusible Ni-complexes.

ings of nucleolar localization of nickel in rhabdomyoblasts and fibroblasts and our findings that nickel is bound to a RNA polymerase-chromatin complex isolated from hepatocyte nuclei of rats which were treated with nickel carbonyl.[10, 111] *Third,* Treagan and Furst[120] have shown that, in tissue cultures of mouse L929 cells, Ni^{2+} inhibits the synthesis of antiviral protein and interferon, in response to innoculation with Newcastle Disease Virus. From these observations, they infer that nickel might also inhibit the synthesis of repressors of tumor viral replication. *Fourth,* Basrur and coworkers[5, 114] have found that Ni_3S_2 inhibits mitotic activity and induces abnormal mitotic figures in tissue cultures of rat embryo muscle cells. Their findings suggest that nickel may interfere with gene replication and the control of cell division. *Fifth,* Swierenga[113] has found that, in tissue cultures of rat embryo muscle cells, Ni_3S_2 profoundly inhibits glyceraldehyde-3-phosphate dehydrogenase activity, whereas $NiCl_2$ and $NiSO_4$ cause only slight inhibition of this important glycolytic enzyme. Inhibition of glyceraldehyde-3-phosphate dehydrogenase activity results in a shift of energy metabolism to the alternative hexose monophosphate pathway. Swierenga[113] postulates that this alteration of muscle glycolysis may be an initial factor in tumor induction.

Current theories regarding possible mechanisms whereby chemical carcinogens may initiate neoplastic transformation are summarized in table XV, based upon Miller and Miller's 1971 schema,[74] with modifications derived from Huebner and Todaro,[53] Ryser,[88] Weinstein et al,[126] and Jungmann and Schweppe.[61]. The studies of nickel carcinogenesis which have been reported by Sunderman[111] are most consistent with hypotheses I-C, II-A, or II-B; the studies of Treagan and Furst[120] appear to support hypothesis II-B, and the studies of Basrur et al[5, 114] are most consistent with hypotheses I-A or I-B. Thus, despite considerable

TABLE XIII

EVIDENCE RELATED TO MECHANISMS OF NICKEL CARCINOGENESIS

I. *$Ni(CO)_4$ inhibition of RNA-polymerase activity in hepatocytes.*[9,10,107,130] Intravenous injection of $Ni(CO)_4$ in rats causes inhibition of liver RNA synthesis as measured (1) *in vitro* in intact hepatic nuclei; (2) *in vitro* by chromatin-RNA polymerase aggregate isolated from nuclei; and (3) *in vivo* by incorporation of ^{14}C-orotic acid into liver RNA.

II. *Ni-binding to DNA, RNA, and nucleoproteins in rhabdomyoblasts.*[47,124] In Ni-induced rhabdomyosarcomas, 70 to 90 percent of intracellular Ni is located in the nucleus, where it is bound to DNA, RNA and nucleoproteins. Nucleolar fraction contains 53 percent of nuclear Ni.

III. *Ni-inhibition of anti-viral protein and interferon synthesis.*[120] In tissue culture of mouse L929 cells, Ni^{2+} inhibits synthesis of antiviral protein and interferon, in response to innoculation with Newcastle Disease Virus.

IV. *Ni-interference with cell division.*[5,114] In tissue culture of rat embryonic muscle cells, Ni_3S_2 inhibits mitotic activity and induces abnormal mitotic figures.

V. *Ni-alteration of energy metabolism.*[113] In tissue culture of rat embryonic muscle cells, Ni_3S_2 inhibits glyceraldehyde-3-phosphate dehydrogenase activity, resulting in a shift of energy metabolism to the hexose monophosphate shunt.

TABLE XIV

RESUME OF THE ACUTE BIOCHEMICAL EFFECTS OF NICKEL CARBONYL IN RATS

Experimental Systems	*Observed Activities (% of Control Values)**	
	Control Rats	*$Ni(CO)_4$-Treated Rats‡*
Hepatic tryptophan pyrrolase activity after tryptophan induction[100]	100 ± 17 (7)	100 ± 12 (7)
Hepatic tryptophan pyrrolase activity after cortisone induction[100]	100 ± 6 (27)	72 ± 7† (9)
Hepatic benzopyrene hydroxylase activity after phenothiazine induction[99]	100 ± 8 (25)	45 ± 8† (9)
Hepatic cytochrome P_{450} concentration after phenobarbitone induction[101]	100 ± 4 (16)	48 ± 5† (9)
^{14}C-Leucine incorporation *in vivo* into hepatic microsomal protein[104]	100 ± 5 (16)	82 ± 6† (11)
^{14}C-Orotic acid incorporation *in vivo* into hepatic RNA[9]	100 ± 14 (9)	25 ± 2† (8)
RNA polymerase activity in intact hepatic nuclei[107]	100 ± 6 (7)	40 ± 7† (8)
RNA synthesis *in vitro* by chromatin-RNA polymerase complex from hepatic nuclei[10]	100 ± 9 (18)	49 ± 6† (18)
Template activity of hepatic chromatin for RNA polymerase from *M. lysodeikticus*[8]	100 ± 9 (6)	87 ± 12 (5)
Template activity of hepatic DNA for RNA polymerase from *M. lysodeikticus*[8]	100 ± 12 (6)	98 ± 6 (5)

* Expressed as mean ± SEM, with number of rats in each experiment group in parentheses. Values marked with a dagger differ significantly from the control values.

† $P < 0.01$.

‡ $Ni(CO)_4$, 2.2-mg per 100 g body weight administered intravenously 6 to 28 hr before sacrifice.

speculation,[27, 28, 30, 113, 128] there is currently little understanding of the exact mechanisms whereby nickel compounds exert their carcinogenic actions.

Nickel as a Possible Carcinogen in Tobacco

The amount of nickel in cigarettes has been measured by seven groups of investigators.[16, 25, 73, 82, 98, 115, 122] As summarized in table XVI, the reported mean values for the nickel content of cigarettes from various sources have ranged from 2 to 6.2 μg. Analyses by Sunderman and Sunderman[98] and Szadkowski and coworkers[115] have shown that 10 to 20 percent of the nickel which is present in cigarettes is released into the mainstream smoke. Based upon the measurements which are summarized in table XVII, an individual who smokes 40 cigarettes per day might inhale approximately from 1 to 5 mg of nickel per year. According to Szadkowski and associates,[115] an average of 84 percent of the nickel in mainstream smoke is present in the gaseous phase, and only 16 percent is present in the particulate phase. Sunderman and Sunderman[98] speculated that gaseous nickel in mainstream smoke occurs in the form of nickel carbonyl. Furst[27] and Wynder and Hoffmann[123] objected to this suggestion on the grounds that nickel carbonyl would readily decompose in tobacco smoke. This objection has been weakened by subse-

quent evidence[62, 108] that nickel carbonyl is more stable in air, breath and biological fluids than had previously been suspected. However, there is to date no definite evidence regarding the chemical form of the vaporized nickel compound(s) in mainstream cigarette smoke.

Measurements of the nickel which is present in various other tobacco products are listed in table XVIII. American pipe tobacco, cigars and snuff have been reported to contain approximately 2 to 3 μg of nickel per gram of tobacco. Fresh and associates[25] have found that Formosan cigars contain an average of 8.5 μg of nickel per gram. Baumslag and coworkers[7] have found that three varieties of South African "Swazi" snuff are grossly contaminated with nickel and other metals. Swazi snuff consists of an admixture of powdered tobacco with the ash of incinerated herbs. On the basis of epidemiological evidence, Baumslag et al[6, 7] have suggested that nickel and other metals which are present in Swazi snuff may contribute to the prevalence of carcinomas of the nose and accessory sinuses among Bantu males.

Carcinogenic Hazards of Nickel Implants

Nickel-containing alloys have been implanted in man and animals in a wide variety of therapeutic devices and prostheses, including (1) stainless steel and nickel wires as suture materials,[131] (2) stainless steel orthopedic implants[3a, 23a, 71b] (3) nickel-chrome metallic mesh for nasal prostheses,[78] (4) stainless steel heart valve prostheses,[91] (5) nickel wire as an intrauterine contraceptive device,[15] (6) nickel-cadmium batteries for implantable cardiac pacemakers[51] and (7) nickel alloys[43, 45, 93] for dental castings and filling materials. Although it has generally been assumed that

TABLE XV

CURRENT HYPOTHESES REGARDING CHEMICAL INITIATION OF CARCINOGENESIS
(Modified from Miller and Miller[74])

I. *Genetic Mechanisms*

A. Direct modification of existing DNA ("somatic mutation") in which replication of chemically altered DNA causes heritable modifications of the DNA nucleotide sequence, causing permanent changes in growth regulation.

B. Alteration of DNA polymerase which temporarily decreases the fidelity of DNA replication, causing mutations of the DNA genome.

C. Chemical modification of RNA which is subsequently transcribed into DNA that becomes integrated in the host genome. This may involve viral RNA-primed DNA polymerase ("reverse transcriptase").

II. *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 tumor viruses or oncogenes.

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

TABLE XVI

NICKEL CONTENT OF CIGARETTES

Authors	*Date*	*Source of Cigarettes*	*No. of Brands*	*μg Ni/cigarette (mean and range)*
Cogbill and Hobbs[16]	1957	American	5	2.0
Voss and Nicol[122]	1960	British	11	6.2 (3.6–11.0)
Sunderman and Sunderman[98]	1961	American	6	2.2 (1.6–3.1)
Fresh et al[25]	1967	American	15	5.4 (0.2–11.6)
		Formosan	12	4.3 (1.1–14.0)
Szadkowski et al[115]	1969	German	8	2.3 (1.1–3.2)
Menden et al[73]	1972	American	2	5.9 (4.3–7.6)

nickel in stainless steels is biologically inert, Ferguson and coworkers[24] have reported that intramuscular implantation of cylinders of stainless steels in rabbits resulted in increased nickel concentrations in parenchymal tissues. Moreover, Mears[72] has demonstrated by electron microprobe analysis that nickel is liberated into human tissues adjacent to implants of stainless steel rods. The nickel concentration was consistently highest at the tissue edge adjacent to the implant. Mears[72] has also found that tissue culture cells (fetal rat dermal fibroblasts) which were grown on grids of stainless steel, accumulated nickel which was clearly demonstrable by electron microprobe analysis. Mears[72] concluded that stainless steel yielded nickel corrosion products in the interstitial fluid which in turn became associated with the tissue culture cells. The development of cutaneous allergic reactions to nickel in human subjects following implantation of stainless steel and vitallium orthopedic devices provides further evidence that such alloys are not biologically inert.[3a, 71b]

There is a paucity of evidence concerning the carcinogenicity of implanted nickel alloys in experimental animals. Mitchell[75] implanted pellets of nickel-gallium dental filling material subdermally in Wistar rats, and found that sarcomas developed at one or more implantation sites in 9 of 10 rats. For comparison, local sarcomas developed in 5 of 10 rats which received implants of pure nickel. No sarcomas developed in any of 10 other experimental groups of 10 rats each, which received implants of a diverse selection of other materials which have been used in dentistry. According to Hueper[57] "the evidence on hand indicates that metal implants which contain nickel and which remain over long periods in human tissues might create delayed potential cancer hazards to their recipients." Two clinical case reports have been published which support Hueper's warning. In a patient described by McDougall,[71a] a sarcoma developed in the soft tissues of the arm, 30 years after implantation of a steel plate. In a patient recently described by Dube and Fisher,[23a] a hemangioendothelioma developed in the tibia and soft tissues of the leg, 30 years after implantation of a steel

TABLE XVII

PARTITION OF NICKEL DURING CIGARETTE SMOKING

Authors	*Date*	*Cigarettes*	*Nickel (μg per cigarette [mean ± std. dev.])*				
			Total Ni	*Ash and Butt*	*Mainstream Smoke*	*Gaseous Phase*	*Particulate Phase*
Sunderman and Sunderman[98]	1961	1 American brand	1.85 ± 0.22	1.32 ± 0.23	0.37 ± 0.16		
Pailer and Kuhn[82]	1963	1 Austrian brand			0.1		
Szadkowski et al[115]	1969	8 German brands*	2.340 ± 0.650	1.140 ± 0.780	0.225 ± 0.142	0.190 ± 0.140	0.035 ± 0.024
Menden et al[73]	1972	Kentucky reference cigarettes	4.25 ± 0.18	3.14	†	†	0.08
		1 American commercial brand	7.55 ± 0.50	6.71	†	†	0.02

* Including 5 brands of cigarettes with filters.

† Menden et al[73] measured nickel in the particulate phase, but they neglected to measure nickel in the gaseous phase.

TABLE XVIII

NICKEL CONTENT OF VARIOUS TOBACCO PRODUCTS

Authors	*Date*	*Product*	*Source of Product*	*No. of Varieties*	*Ni Content (μg/gm) (mean and range)*
Sunderman and Sunderman[98]	1961	Pipe tobacco	American	1	2.7
		Cigars	American	1	3.2
Fresh et al[25]	1967	Cigars	Philippine	3	2.8 (1.9–3.9)
		Cigars	Formosan	3	8.5 (3.6–15.0)
Baumslag et al[7]	1971	Snuff	American	3	2.3 (2–3)
		Snuff	South African	3	52 (43–87)
Baumslag and Keen[6]	1972	Snuff	South African	3	88 (58–112)

plate. In both of these patients, the implanted steel plate was fabricated of an alloy which differed from that of the screws which were used to fix the plate *in situ*. Such conjoined surgical implantation of metals that are of dissimilar composition may result in unnecessary electrolysis and metallic corrosion.[23a] Dube and Fisher[23a] speculated that metallic corrosion products, including nickel and chromium, were responsible for the induction of the hemangioendothelioma in their patient.

Conclusions

The epidemiological and experimental data which have been summarized in this paper provide conclusive evidence of the carcinogenicity of certain nickel compounds. In addition to the obvious hazards to workmen in the nickel industries, nickel carcinogenesis may represent a widespread hazard to the general population, since tobacco products have been shown to contain appreciable concentrations of nickel, and since the parenteral implantation of nickel alloys is becoming common. Data which have been reviewed elsewhere[103] suggest that atmospheric contamination with nickel and the presence of nickel in asbestos fibers may also pose carcinogenic hazards. From a methodological viewpoint, nickel carcinogenesis affords an attractive experimental model for further research into mechanisms of chemical carcinogenesis, inasmuch as the carcinogenic nickel compounds are (1) structurally simple, (2) inexpensively available in high purity and (3) readily labelled with ^{63}Ni, a beta-emitting radioisotope with a long half-life, which is ideally suited for liquid scintillation spectrometry and autoradiography.

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My Daily Prayer

O Lord, Help me to keep my big mouth shut until I know about what I am talking.
