Chicago and was about one-half of the mass collected in homes where the windows were kept open. In the progression from an urban to a rural environment, the average mass collected in the 30-day period decreased by about a factor of 2.

Figure 4 compares the masses collected in various rooms of the home. The values corresponding to the bathroom and the kitchen measurements are significantly higher than for the other rooms. Kitchens with gas stoves (38) contained more than the overall average particulate mass, and those with electric stoves (18) contained less. In the progression from rural to urban areas, for homes with closed windows, the relative comparison between rooms did not change, and the particulate concentrations in the suburban homes were approximately the same as the overall averages, with the rural areas contributing less and the urban areas contributing more.

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4. In order to reject measurements which might have come from damaged or contaminated foils, a two-step procedure was used. First, we calculated the mean and standard deviation by using all of the measurements; then any measurements lying more than 2 standard deviations from the mean were omitted, and the remaining sample was used to calculate a new mean and standard deviation. This procedure usually resulted in the rejection of approximately 10 percent of the events and gave a significant decrease in the standard deviation. The fractional uncertainty, that is, the standard deviation over the mean, is between 50 and 80 percent for most of the averages computed.
5. The rate of particulate fallout is given in milligrams per foil per month and can be easily converted to other measures of the rate of sedimentation. For example, 1 mg per foil per month is approximately equal to 1 pound per 1000 square feet per year.
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Copper on Intrauterine Devices Stimulates Leukocyte Exudation

Abstract. *Metallic copper in the uterine or abdominal cavities of rats or monkeys stimulates an impressive local exudation of polymorphonuclear leukocytes. This cellular response to copper persists for at least 7 months, without significant local tissue damage or detectable systemic effects on the test animal. This finding provides a possible explanation for the capacity of copper to increase impressively the antifertility effect of polyethylene intrauterine contraceptive devices.*

Metallic copper has been shown to exert a potent antifertility effect in the uterine cavity (*1*). The pregnancy rate in women using the "Tatum T" plain polyethylene intrauterine contraceptive device was found to be 18 percent per year, whereas this rate was reduced to 0.5 percent or less by addition of a coil of fine copper wire (200 mm^2 surface area) to this device. A fine copper wire placed in the lumen of one rat uterine horn completely prevented pregnancies in that horn, without influencing the number of fetuses in the control horn, an indication that the copper wire was acting locally, not systemically, to produce an antifertility effect. The mechanism of action of copper in this situation is unknown.

Parr and colleagues (*2*) have demonstrated a correlation between mobilization of leukocytes into the uterine cavity and the efficacy of various types of intrauterine contraceptive devices. The evidence indicated that the persistent low-grade inflammation with accompanying leukocyte emigration resulted in local conditions toxic for the fertilized egg. El Sahwi and Moyer (*3*) have found a quantitative relation between the presence of leukocytes and the antifertility effect.

We now report observations in rats and monkeys on the local mobilization of leukocytes in response to implantation of polyethylene or metallic copper devices. The devices were inserted aseptically into the uterus or into the abdominal cavity. At intervals from 10 days to 7 months smears were made of the surface coatings of the devices, and the adjacent tissues were fixed for study by light and electron microscopy.

The results (Table 1 and Figs. 1 and 2) show that metallic copper alone or a copper-clad polyethylene device in the

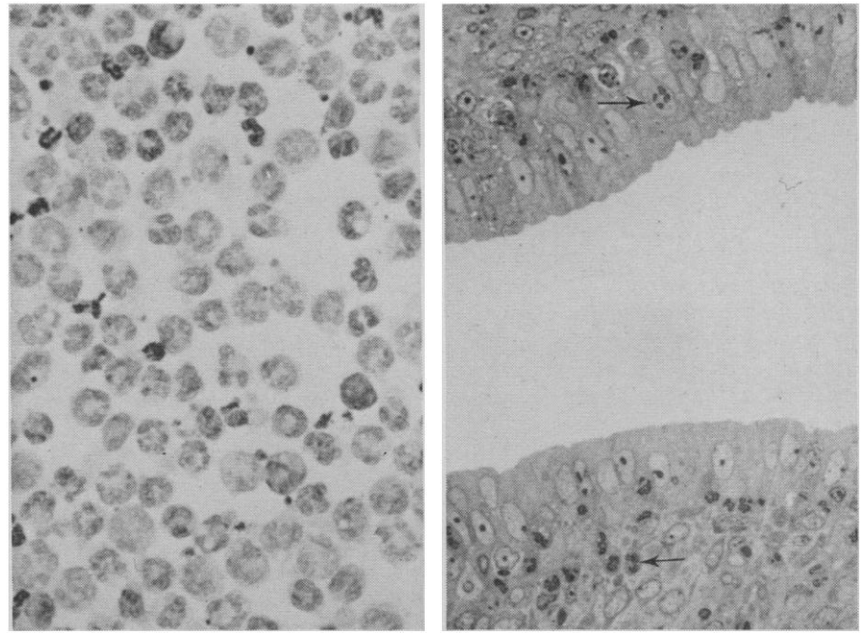

Fig. 1 (left). Smear of surface of a copper wire that had been in a rat uterine horn for 10 days. Numerous polymorphonuclear leukocytes are seen. [Tissue was air dried, and Wright-Giemsa stained (×412)]. Fig. 2 (right). Rat uterine horn fixed 10 days after insertion of a thin copper wire. The lumen (open space) and endometrium are shown. Numerous polymorphonuclear leukocytes (arrows point to examples) are seen in the stromal and in the surface epithelial layers. Fixed with glutaraldehyde and osmium, and embedded in Epon; thick section stained with azure A at alkaline *p*H (×128).

Table 1. Mobilization of polymorphonuclear (PMN) leukocytes in the uterine or abdominal activities in response to metallic copper; IU, intrauterine; IA, intraabdominal.

Device	Site	Time in place (mo)	PMN*
	Rats		
None	IU		0
Copper	IU	~1/3	+++
Polyethylene	IA	3	0–+
Polyethylene + Cu	IA	3	++++
	Monkeys		
None	IU		0
Polyethylene	IU	7	0–+
Polyethylene + Cu	IU	7	+++
Polyethylene	IA	3	+
Polyethylene + Cu	IA	3	++++

* PMN infiltration or exudation at or near device as estimated from microscopic examination.

abdominal or the uterine cavities of both rats and monkeys induced an impressive accumulation of leukocytes on the surface of the device and in the neighboring tissues. These leukocytes were mainly neutrophils; small numbers of eosinophils and macrophages were also present. In contrast, leukocyte accumulation in response to plain polyethylene devices was scanty or absent. The cellular response to copper persisted for at least 7 months, without detectable local tissue damage or systemic effects on the host. The mechanism by which copper induced the local accumulation of leukocytes is not clear. Previous studies (*4*) have shown that metallic copper is very slowly dissolved in the uterine cavity; presumably the cuprous ions then interacted with tissue components to produce conditions chemotactic for neutrophil leukocytes.

The means by which polymorphonuclear leukocytes or products liberated from these cells exert an antifertility effect in the uterine lumen is not known. In some situations products liberated from disrupted leukocytes, or other cells, have been shown to interfere with maturation or even with survival of the newly fertilized egg (*5*). Thorough studies have not yet been made of other possible antifertility effects, such as spermicidal action or interference with implantation.

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2 August 1971

Diurnal Rhythm in Endoplasmic Reticulum of Rat Liver: Electron Microscopic Study

Abstract. *Electron microscopy of rat hepatocytes revealed a diurnal variation in the relative amounts of endoplasmic reticulum structures and regional differences in their distribution within the hepatic lobule. The diurnal changes in smooth and rough endoplasmic reticulum structures were compared with the diurnal changes in the hepatic microsomal enzyme hexobarbital oxidase. In the control group, at the time when enzyme activity was maximum, the amount of smooth endoplasmic reticulum was also maximum and vice versa. When the enzyme rhythm was abolished, as in blinded rats, the diurnal rhythm in the endoplasmic reticulum was also abolished.*

Many drug-metabolizing enzymes are localized in the microsomal fraction of liver homogenate (*1*). The microsomal fraction is composed of fragments of endoplasmic reticulum (ER), which, by electron microscopy, appear to consist of smooth- and rough-surfaced structures. The development of pharmacologic procedures that alter the activities of these drug-metabolizing enzymes has permitted electron microscopic studies of the associated changes in the morphology of the ER. For example, agents such as 3,4-benzopyrene, 3-methylcholanthrene, phenobarbital, aminopyrine, and phenylbutazone, when given to rats, produce a rapid increase in the activity of many enzymes, as determined chemically in the microsomal fraction (*2*), and, concomitantly, produce ultrastructural changes in the ER (*3*) of intact liver cells. In phenobarbital-treated rats, Remmer and Merker found an increase in smooth ER, and this increase reached a maximum when the enzyme activity was highest (*3*). Similar results were noted with other enzyme inducers—tolbutamide, nikethamide, phenylbutazone, and meprobamate (*4*).

Others have also found a relation between the induced enzyme synthesis and the stimulated formation of ER membranes (*5*, *6*). Dallner *et al.* have studied the relation between microsomal enzyme activities and ER membranes in early development (*7*). The activity of many of these enzymes is low at birth and increases at different rates soon afterward. Extensive synthesis of microsomal membranes occurs in the livers of rat fetuses toward the end of gestation. These appear first as rough-surfaced ER. After the fetus is born, two different processes take place: (i) the production of a large amount of smooth ER membranes and (ii) the appearance of membrane-bound enzyme activities in a characteristic temporal sequence. The implication of the findings of Dallner *et al.* (*7*) is that the ER can be a dynamic rapidly changing structure.

A daily rhythmicity has been observed for some of the hepatic drug-metabolizing enzymes (*8–10*). For hexobarbital oxidase (HO) and *p*-nitroanisole-*O*-demethylase (OD), Nair and Casper (*9*) found that, in rats, the enzyme activities were high in the night (10 p.m. and 2 a.m., respectively) and low during the day (2 p.m. and 6 p.m., respectively). For HO, the values at 10 p.m. were 44 percent higher than those at 2 p.m. and for OD, the 2 a.m. values were 52 percent higher than those at 6 p.m. The results from measurements in vitro of HO activity in the microsomal fraction have been further supported by parallel determinations in vivo of the duration of sleep induced by hexobarbital. Furthermore, Nair *et al.* (*10*) noted that the rhythmicity of enzyme activity is abolished in animals exposed to continuous illumination, continuous darkness, or blinding. In these experiments, animals were killed every 4 hours.

Thus studies by electron microscopy have revealed changes in the endoplasmic reticulum parallel to the alterations in hepatic microsomal enzyme activity. Previous investigators have examined the changes associated with (i) the normal developmental increase in enzyme activity taking place during growth and (ii) the increase in activity brought about by chemical inducers. The findings of a diurnal variation in enzyme activity provide another experimental