# THE EXCRETION OF DRUGS, PESTICIDES, AND RADIONUCLIDES IN MILK

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In a previous article in 1947, the author[55] dealt with the limited information available on the excretion of drugs in human milk; subsequent articles by others[42,33] have indicated the same state of affairs. In spite of the tremendous increase in the number and use of therapeutic agents in the last decade a study of the recent literature reveals that little work has been done on their excretion in milk. In the present article an account is given of the information that has become available since 1947. A previous statement[55] still holds, that there is no information at all on the excretion in milk of many substances used in therapeutics, and that details about others on which reports have been made are very inadequate. Although it is clear that the excretion of many drugs in the milk has not been examined it should also be noted that many drugs will not appear in the milk because they are rapidly bound to plasma protein, inactivated, or cleared.

Consideration is also given in the present article to the possible dangers from cow's milk. The widespread use of fresh and dried cow's milk which may nowadays contain antibiotics, insecticides and radio-active substances necessitates the fullest investigation and constant surveillance of all milk preparations.

Attention is drawn to the following useful articles on the composition of normal milk. A detailed account of 73 components of human colostrum and milk with many references to the literature is given by Macy.[40] Clinical and chemical studies on human milk during lactation are reported by Hytten[30,31] and Hytten and Thomson.[32] The influence of diet and special feeds on the composition of cow's milk is reviewed by Petersen.[52] The chemical composition of breast milk, and of cow's, goat's and sheep's milk is given in full detail in Documenta Geigy (*Scientific Tables*).[20]

## *Pharmacological Data*

*Fluids* administered in large amounts to women (at least 6 pints a day) do not increase milk production and may actually reduce it.[34]

*Food constituents.* The milk may acquire the odour of alliaceous oils when these are present in the mother's food. Cow's milk may taste of onions or smell of garlic when the animals have eaten onion grass or wild garlic.[52] When animals are given large amounts of cod-liver oil the milk may taste and smell of fish oil. There is little evidence that any products from fruit and vegetables enter the milk and cause symptoms in the baby. However, protein substances may be responsible for allergic reactions in the sensitive child, for instance, from egg albumin. The milk of mothers suffering from beri-beri is stated to be 'toxic' to the child,[33] but protection would be afforded by giving proper food.

*Antibodies* are present in human colostrum and in mature milk but they apparently do not survive digestion in significant quantities. In the human species the transfer of antibodies across the placenta is much more important than their ingestion in colostrum and in mother's milk. The presence of Rh antibodies in human milk was first demonstrated by Witebsky *et al.*[65] They found that the titre is usually low and that breast feeding causes no continued haemolysis of the baby's red cells. The titres of various antibodies in milk have been correlated with those in the blood stream by Davidsohn.[19] All blood-group antibodies, including the Rh agglutinins, may be excreted in the milk, and it is possible that a newborn infant with haemolytic disease may be further injured by the mother's milk; Dahr and Wolf[18] state that infants with erythroblastosis should not be nursed by their mothers. The view has been held for decades that infants with erythroblastosis do not thrive on their mothers' milk but this theory does not appear to be accepted nowadays; antibodies present in the mother's milk are inactivated in the intestinal tract and do not cause further haemolysis of the infant's red blood corpuscles. Immunity to the Coxsackie group of viruses is transmitted from vaccinated mice to their offspring in the colostrum or milk.[46]

## *The Excretion of Drugs*

Depressants of the nervous system were considered previously[55] and there is little to add today except for the following details. Other groups of drugs are dealt with more fully.

*Chloral hydrate* administered in suppositories to nursing mothers was found, together with its metabolites, within 15 minutes and for up to 24 hours in the milk in levels lower than that in the maternal blood and in insufficient amount to affect the infant adversely.[3]

*Morphine* is not excreted in the milk or, if excreted, in insignificant amounts. The characteristic odour of opium may be transmitted to the milk.[59]

*Pethidine* is not excreted in the milk of rats.[59]

*Caffeine* is secreted in the milk, and may cause restlessness in some infants.[62] The widespread consumption of caffeine in various hot and cold drinks warrants further investigation of this subject.

*Nicotine* was previously considered[55] and shown to be a rare cause of symptoms in the breast-fed infant. Further references on nicotine are given by Goodman and Gilman.[26]

*Antihistamines* or their breakdown products only pass into the milk in minimal amounts and produce a lactagogue effect within 1 hour after injection, which is maintained for 24 – 72 hours.[53]

*Fluoride* was found rather constantly in milk at about one-third of the level in the mother's blood.[28] The level was not influenced by the ingestion of fluorides by the mother; for example, when sodium fluoride was taken in doses of 10 mg. daily for 5 days the maternal level increased but the amount in the milk remained approximately the same.

*Iron* is present in human milk to the extent of about 2·5 mg. per litre and in cow's milk, on an average, 0·5 mg. per litre. The amount in cow's milk is not influenced by the administration of iron to the animal. In puerperal women the administration of iron leads to an increase in the daily elimination of iron in the milk, reaching a peak about the 7th day of the puerperium, and more marked in primiparae than in multiparae.[24] The iron supplies of the

newborn infant may possibly be increased in this way by giving iron to lactating women.

*Folic acid* increases lactation in nursing rats, and liver is still more efficient in this respect.[48]

*Dicoumarol* administered in large doses to lactating rats, has produced haemorrhages and death in the suckling rats.[25] In rabbits the excretion of dicoumarol in the milk depresses the prothrombin index of the litter to a level lower than that of the mother.[23] When full controlled therapeutic doses are given to women some of the anticoagulant is secreted in the milk, but without significantly altering prothrombin activity in the infant.[1,7] On the other hand, Christ[10] states that dicoumarin derivatives pass readily into woman's milk and may cause harmful effects, including liver damage, in the infant; he concludes that ethyl biscoumacetate (tromexan) and other dicoumarol derivatives should not be given to women who are breast-feeding their infants.

*Vitamin A* increases considerably in the milk of normal lactating women within 12 hours after administration in aqueous dispersion, but the increase is much smaller when the same vitamin is given in oily solution; the aqueous preparation also produces higher blood levels, indicating good absorption.[58] The occurrence of carotenoderma in mother and infant was previously reported.[61]

*Vitamin D* in milk can be increased to an antirachitic amount by giving large doses to the mother.

*Tocopherol* added to the feed of dairy cows increased the fat content and the yield of milk.[27] According to Neuweiler[49] cow's milk contains vitamin E in amounts of 18 – 152 micrograms per 100 ml. and human milk 280 – 3000 (average 1000). Overdosage with 240 mg. of vitamin E (ephynal) daily only raised the milk to a higher physiological level. The needs of a suckling baby were estimated to be about 5 mg. a day, and this must come mainly from the food; it should be noted that cow's milk contains only a small amount of the vitamin.

*Ascorbic acid* can be increased up to 6 times its previous concentration when the maternal diet is rich in the vitamin but, under the best conditions, 8 mg. per 100 ml. is the maximum amount in breast milk.[11] Human milk usually contains 2 – 6 mg. per 100 ml.

*Pyridoxine* in human milk can be increased considerably by oral administration of this vitamin.[50]

The vitamin content of human milk and its fluctuations according to diet and supplements were studied during the War by Kon and Mawson.[37]

*Thyroxine* or iodinated products given to cows stimulate milk production and increase the amount of fat, lactose, and phosphorus, but little if any thyroxine is present in the milk and it is safe and suitable for human consumption.[5] In pregnant rats the administration of large amounts of thyroxine does not cause its secretion in a physiologically active form.[29]

*Antithyroid drugs*, both thiouracil and imidazole compounds, are excreted in high concentration in milk. In women the milk may contain 3 times as much thiouracil as the blood.[33,64]

*Iodide* is normally present in milk in small amounts, and the quantity is increased after oral administration of iodine compounds.

*Radio-active iodine* has been demonstrated in the milk of lactating mothers after oral administration of tracer doses of the isotope. The amount in the milk may be considerably higher than that in the plasma, i.e. there is selective concentration in the milk.[47] The risk of adverse effect on the infant thyroid is considerable. Nurnberger and Lipscomb[51] demonstrated a significant uptake by the thyroid glands of suckling infants. They also refer to earlier experimental work in mice and rabbits and other animals in which not only radio-iodine but also other isotopes such as radiocalcium, radiostrontium, radio-iron, and radiosodium were shown to be transmitted in the milk. In goats it has been found that when sodium radio-iodide is administered orally an average of 50% of the dose is found as iodide in the milk, and none is present as thyroxine or other organic compounds.[66]

*Copper* is present in human milk in concentrations up to 0·28 mg. per litre. In cow's milk the average concentration is 0·15 mg. per litre and this is not increased by giving 5 times the normal amount in the food. In rats the milk contains 10 times as much copper as the milk of other species.[59]

*Selenium* has been demonstrated in the milk of cows in seleniferous areas. In white rats injected with sodium selenate (containing radio-active selenium) the selenium is found in the milk bound to the proteins.[43]

*Thallium* may be present in toxic amounts for sucklings in fatal cases of thallotoxicosis.[12]

*Sulphonamides.* The excretion of these chemotherapeutic drugs into human milk received much attention in previous years.[55]

*Antibiotics* administered to cows pass from ingested food into the blood stream and thence into the milk. Some workers[56] reported that no penicillin was found in the milk of cows given intravenous injections of the drug, but others[35] describe the levels of penicillin in the milk after intramammary injection during the lactation period. The following antibiotics could be demonstrated in cow's milk after treatment of the animal for mastitis, but in amounts unlikely to modify oral or intestinal flora or resistant strains or to provoke sensitization: penicillin, detectable for 6 days; streptomycin, for 1 day; oxytetracycline, for 3 days, and chlortetracycline, for 3 weeks.[63] Penicillin has been found in human milk in significant amounts within 1 hour after injection, thereafter increasing in concentration to 4 hours and then gradually falling.[54] Streptomycin is excreted in the milk. Chloramphenicol reaches levels in the milk of human beings of about one-half those in the blood.[57]

Many authorities consider that the presence of antibiotics in milk and milk products may sensitize certain individuals and even perhaps cause reactions. This problem is important, especially in connection with penicillin, and steps have been taken to avoid this hazard.[21, 44]

*Organic arsenicals* given by parenteral injection are excreted in small amounts in the milk, and *mepacrine* in negligible amounts.[26]

*Pesticides*

*Phosphate-ester insecticides* are among the most toxic chemicals commonly used for pest control. They are not used on livestock.[13] One of these anticholinesterases named parathion was administered in capsules to dairy cows but did not pass into the milk and produced no harmful effects in the animals.[17]

*Dicophane* (DDT) is a chlorinated insecticide which is excreted in measurable amount in the milk of dairy animals which eat fodder from fields dusted with this compound. The milk may be lethal to insects and may produce typical symptoms in the sucklings of white rats and goats.[60] The milk of cows fed on sprayed alfalfa contained about 3·5 mg. per litre, which diminished in 10 days but persisted for 4 – 6 months after withdrawal.[4]

*Gamma benzene hexachloride* (lindane) is eliminated in the milk of lactating animals, most of it within 24 hours after administration is stopped. It is rapidly excreted and completely disappears from the animal's body within one or two weeks.[14]

*Toxaphene* is a chlorinated camphene used to destroy ticks and mites. It may be excreted in the milk.[15] It should not be used on dairy cattle or in barns.

*Chlordane*, fed to lactating rats, causes the milk to be toxic to the suckling. There is danger associated with its ingestion and retention in milk, or in the body tissue of dairy animals, poultry, or meat animals.[16] *Dieldrin*, another indane derivative, passed into the milk when sprayed on cows at 3 - week intervals but the amount gradually decreased, regardless of its continued application.[8]

*Phenothiazine* has been used as an insecticide and as an anthelmintic in livestock. It caused the milk of nursing goats to undergo pinkish discolouration when exposed to the air for several hours.[22]

*Radio-active Substances*

Reference has been made above to radio-active iodine and other isotopes.

Radio-active materials (radionuclides) created as the result of nuclear detonations (atomic bombs) have been carried to the stratosphere and return slowly to earth with rain, snow and dust particles. One danger is their passage through the soil into plants. In cows the milk can become radio-active from this source. There is constant need for radiation surveillance of milk, dairy products, and other foods. Any determined values and variations must be considered tentative and subject to change when estimates are made of the possible hazards associated with the long-term use of radio-active milk.

The fall-out of radio-active strontium, its presence on grass, its absorption into animals, and the concentration in milk, and in the bones of sheep, have been measured in England.[45] The amounts estimated in hay and milk have this year been published by Booker.[6] About 1/7th of the strontium-90 ingested by the cow appears in her milk. Experimentally it has been demonstrated in lactating rabbits that radio-active strontium passes through the milk to the suckling; the peak of excretion in the milk occurs when the level in the blood is low.[36] In lactating guinea pigs the intramuscular injection of radiostrontium causes its appearance in the long bones of the sucklings.[41]

The presence of caesium-137 and the variation in amount of this radionuclide in dried milks in England is revealed by Booker.[6] It appears to be derived mostly from direct fall-out on the herbage and little from the soil.

In the USA dried milk is sampled from numerous places for caesium-137 and potassium-40 as a routine measure. Traces of these isotopes have been detected in human beings, the main source probably being cow's milk.[2]

In Sweden the presence of caesium-137 in dried milk and soil has been determined[39] and the correlation between caesium-137 and strontium-90 shown to be good, so that the caesium-137 values may be used for estimations of the strontium-90 content, provided their source is atomic-bomb debris.

During periods of local weapon-testing, barium-140 appears prominently in milk.[2] Data have been published this year on the concentrations of radio-active iodine, strontium, barium and caesium in cow's milk in the USA.[9,38] The radionuclide of greatest potential hazard in milk is $^{90}Sr$, followed by $^{131}I$. In addition, further evidence is needed on the contribution of radionuclides in other foods towards total dietary exposure.

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