The metabolic interactions between dietary constituents and drugs are varied and complex. Drugs can adversely affect nutritional status, while nutrients in foods can affect the metabolism of drugs and their therapeutic efficacy and toxicity. In a country like ours, where undernutrition is widespread and where the wide prevalence of several infectious diseases calls for the intensive use of a range of potent drugs, a proper understanding of drug nutrient interactions and their implications is extremely important. Unfortunately this subject has not received the attention it deserves from either physicians or nutrition scientists. In this communication, work carried out in India in recent years (largely at the National Institute of Nutrition, Hyderabad) in this area is briefly discussed.

Before a drug exhibits its activity, it has to get absorbed, bind to plasma proteins and get transported, to be delivered to various organs and target tissues in adequate concentrations. It is only when these processes are complete that a drug can exert its therapeutic (or toxic) response. The fate of the drug in terms of absorption, binding, distribution, metabolism and excretion can be influenced by the patient's diet and nutritional status.

**Absorption**

Considerable attention has been directed to effects of food on absorption of drugs. When a drug is administered orally, it undergoes processes such as disintegration, dissolution, absorption and passage through liver. Foods can affect one or many of these stages. The quantity and quality of foods have been shown to enhance bio-availability of a number of drugs such as antihypertensive (beta-blockers, hydralazine), antibiotics (erythromycin stearate, nitrofurantoin) and anti-convulsants (phenytoin, carbamazepine). For example, high fat diet enhances the absorption of grifulvin and a high protein diet increases propranolol bioavailability. It has recently been demonstrated that rice and wheat diets improve the bioavailability of the anti-malarial drug chloroquine.

Foods can also reduce the absorption of many other antimicrobial agents such as isoniazid, rifampicin, penicillin and ampicillin. Several mechanisms are implicated in such food-drug interactions in the gastro-intestinal tract. Binding of drugs to substances in the food, alterations in pH, gastric emptying time, intestinal transit time, mucosal absorption and splanchic hepatic blood flow account for food-induced variations in absorption of drugs. These variations will directly influence the onset, intensity as well as duration of action of drugs.

Most drugs, in practice, are administered by the oral route and therefore altered absorption would be of clinical significance for drugs such as antibiotics, anti-convulsants, anti-hypertensive and anti-malarial. As a 'general rule, solutions and suspensions are less susceptible to food drug interactions. On the other hand, enteric coated drug preparations are more prone to food interactions. The effect on drug absorption is inversely proportional to the time gap between food intake and drug dosing, being maximal when the drug is taken immediately after meals. Studies on chloroquine and
rifampicin clearly indicate that chloroquine, a gastro-intestinal irritant, has to be administered along with food for better therapeutic efficacy while rifampicin has to be administered on an empty stomach.\textsuperscript{1, 27} Caution needs to be exercised when administering bactericidal drugs which are given once a day depending on the effects of food on their bio-availability. Our studies have shown that malnutrition decreases and delays absorption of antibiotics and nutrients used as medicaments which may result in therapeutic failures.\textsuperscript{30}

**Protein Binding and Volume of Distribution**

An important pharmacokinetic parameter which determines the plasma concentration of a drug is its apparent volume of distribution. This, in turn, is dependent on plasma protein binding. The binding of a drug to plasma proteins is a significant determinant of the intensity and duration of the drug's pharmacological actions and its eventual elimination. Drug protein binding may be expected to vary in varying grades of malnutrition and can change in relation to endogenous nutrient-related substances such as fatty acids, bilirubin, tryptophan, uric acid, etc. which bind to albumin. Significant reduction in binding of several drugs had been documented in malnutrition in both adults and children in several Indian and other studies.\textsuperscript{6, 13, 17}

Clearance of drugs such as phenylbutazone, rifampicin and doxycycline in undernourished subjects has been shown to correlate with protein binding.\textsuperscript{22, 23, 32} In malnutrition, protein binding of the drug propranolol was observed to be higher due to greater amounts of α1 acid glycoproteins.\textsuperscript{10} Our observations on tetracycline in the malnourished indicate that the tissue uptake and binding of this drug is significantly reduced in malnutrition, with a decrease in volume of distribution.\textsuperscript{31} Data on tissue binding of drugs in human malnutrition are, however, generally scanty.

In addition to plasma proteins, in the malnourished humans, there is a reduction in body fat which could also alter the distribution of highly lipid soluble drugs. The consequent elevation of free (unbound) drug concentration with a decrease in the distribution are likely to result in higher toxicity.\textsuperscript{17}

**Detoxification of Drugs**

Detoxification of drugs involves Phase I (oxidation, reduction, hydroxylation) and Phase II (conjugation) processes, mediated by mixed function oxidases. The conjugating enzymes are located in the liver, kidney, lungs, gastro-intestinal tract, placenta, skin and blood cells. The microsomal drug metabolizing enzymes, located in the endoplasmic reticulum, directly determine the rate of metabolism and plasma therapeutic efficacy and toxicity of drugs. These enzymes are also concerned in the detoxification of a wide range of chemicals such as pesticides, mycotoxins, environmental pollutants (carcinogens), cosmetics and dyes. These major enzyme systems with wide substrate specificity, therefore, determine not only the pharmacological, but also toxicological properties of drugs and chemicals.
Most nutrients participate directly or indirectly in the functioning of the above enzymes involved in the detoxification process of the drugs. Literature in experimental nutrition provides ample evidence that nutritional constraints alter drug metabolism. However, experimental data cannot always be extrapolated to human situations for reasons such as species variations and poor predictability of pharmacological effects in experimental nutritional deficiencies. Further, enzyme activity in vitro and clearance of drugs in vivo need not be identical.

In general, experimentally induced nutritional deficiencies, except deficiencies of thiamine and iron, decrease the activity of enzymes involved in drug detoxification. Severe protein and fat (lipoprotein) restriction invariably decrease the enzyme activity. On the other hand, chronic semi-starvation appears to increase the enzyme activity and metabolism of certain drugs.

Studies on Detoxification of Drugs in Humans

Studies on drug detoxifications can be considered under the above two phases of metabolism, namely, oxidative metabolism (Phase I) and conjugation of drugs (Phase II).

**Oxidative Metabolism (Phase I):** Mixed function oxidases involved in Phase I of detoxification were evaluated in malnourished adult subjects by use of prototype and specific drugs such as antipyrine, doxycycline, phenylbutazone and rifampicin. These studies showed that the clearance of these drugs in general was delayed in severe malnutrition as encountered in cases of famine oedema. These results indicate the need for altered dosage schedules particularly in severe malnutrition. Delayed clearance of drugs has been observed in severe states of malnutrition in children viz. kwashiorkor and marasmus.

**Conjugations (Phase II):** Studies in malnourished children using chloramphenicol, paracetamol, sulfadiazine, isoniazid indicate that conjugation reactions are decreased. Peak plasma concentrations are delayed, areas under plasma time concentration curves are higher and steady state levels are increased due to decreased conjugations. Therefore, in malnourished children, drugs such as chloramphenicol could evoke more severe toxic reactions. It is necessary to reduce the dosage in order to have plasma steady state concentrations below the toxic range. However, conjugations of contraceptive steroids are not impaired in undernourished women.

Our recent observations on in vitro enzymes such as benzo (a) pyrene hydroxylase, γ glutamyl transpeptidase, paranitrophenol and glutathione conjugations bring out the reciprocal effects on oxidation and conjugation systems with an increase in oxidation and decrease in conjugation of some substrates which can result in higher toxic effects.

**Metabolic Experiments**

Several metabolic experiments have been carried out to assess the effects of macronutrients on drug clearance. Our studies on varying protein and energy intake
demonstrate that inadequate energy intake (60 percent of recommended dietary allowances [RDA] with 10 percent protein energy) diminishes drug clearance, whereas with energy intakes of 60-70 percent of RDA with 15 percent protein energy, drug kinetics are not altered significantly.

On the other hand, carbohydrate energy with relative deficiency of protein intake (five percent protein energy) diminishes drug clearance even if the total energy intake is adequate (3000 kcal). Asian vegetarians are reported to have lower clearance of drugs whereas Caucasian vegetarians do not differ in drug clearance from non-vegetarians. Data on the protein concentration of the two sets of vegetarian dietaries are necessary to know if the difference is truly ethnic or is related to differences in protein concentration of their dietaries. Studies on protein supplements suggest that isocaloric substitution of proteins for carbohydrate at constant energy intake (40 percent of protein energy) enhances the clearance of drugs such as theophylline and antipyrine. When energy intake is a limiting factor and proteins are used for energy needs as happens in severe protein energy malnutrition, drug clearances will be impaired. Therefore drug doses need to be decreased in severe states of malnutrition. Nutritional status could also influence the clearance of drugs by the kidney.

Renal excretion of drugs has been investigated both in malnourished children and adults. The results suggest that elimination of drugs such as penicillin, cephalixin, gentamicin, tetracycline and tobramycin are reduced in severe states of malnutrition whereas in lesser grades of malnutrition, the drugs are eliminated faster due to decrease in protein binding. These results are similar to those with respect to the hepatic detoxification of drugs. Therefore, in conditions of faster elimination in order to maintain maximum and minimum inhibitory concentrations especially for antibiotics, dosage intervals have to be reduced. Plasma concentrations of nephrotoxic drugs such as gentamicin and other aminoglycosides require to be monitored in severe malnutrition.

**Toxicity of Drugs and Chemicals in Malnutrition**

Nutritional stress seems to be an important determinant of drug toxicity in experimental animals. Hypoalbuminemia has been shown to be associated with greater vulnerability to toxic reaction of drugs. Several recent studies in kwashiorkor indicate that symptoms such as edema, fatty liver and skin lesions can be indirectly attributed to free radical generations arising from impaired detoxifying capacities as the body reserves of antioxidants such as vitamins A and E, beta-carotene and zinc which are protective, are low in malnourished states.

Our recent studies on hepatotoxicity of antitubercular drugs in adults and observations in children confirm that toxic reactions to these drugs are higher in malnutrition, and stress the need for careful evaluation of drug dosage in undernourished subjects, from the point of view of therapeutic efficacy and toxicity. Toxicities in malnutrition seems to be determined by a balance of many events such as the chemical nature of the parent compound and its metabolite, alterations in pharmacokinetic parameters and the receptors. Therefore various permutations and combinations of adverse effects and
efficacy are possible in malnutrition including increased susceptibility to chemical carcinogens.\textsuperscript{11,18} Drug induced nutritional disorders may further complicate and compound the picture.\textsuperscript{8,37}

The studies briefly discussed here provide two important messages:

- Where drugs are being used for the treatment of ailments in undernourished population, the dosage schedules generally prescribed by the manufacturers may need to be reviewed and modified. Currently, this aspect of drug therapy in our country is being totally neglected. As several factors determine the dosage schedules, it is necessary to have a fresh look into doses employed and therapeutic response in undernutrition.

- Undernourished populations are more susceptible to toxic effects of chemicals and potential carcinogens. The problem of environmental pollution therefore must claim even greater concern in the context of widespread prevalence of undernutrition. It is possible that several important factors of clinical importance remain unrecognized and therefore warrant further research.

\textit{The author is Deputy Director, National Institute of Nutrition, Hyderabad.}

References