by DMAE, and the threshold at which reticular stimulation induced this type of cortical activity was lowered (*13*). In standardized tests of emotionality, mice on DMAE 0.05 percent in drinking water (*ad libitum*) showed an increase in emotionality which was significantly different from the control mice. Maze learning of rats and mice on DMAE is not facilitated (*13*).

In rats and dogs, DMAE in doses up to 7.5 mg/kg does not produce an antidiuretic effect or a change in renal hemodynamics (*13*). Single doses of 500 mg/kg of DMAE do not protect mice from lethal doses of *d*-tubocurarine, decamethonium, atropine, or hexobarbital.

Since DMAE may occur in natural foods and may regulate the synthesis of acetylcholine, the cautious clinical trial of various salts of DMAE was initiated. Total oral doses as low as 10 to 20 mg of DMAE base per day produce, in 7 to 10 days, a mild and pleasant degree of central nervous system stimulation which is characterized by lessened daytime fatigue and sounder sleep, but fewer hours of sleep are needed. Doses above 20 mg/day may result in increased muscle tone (most evident in the neck, masseter, and quadriceps muscles) and insomnia. (This observation contrasts sharply with that for choline, where 10 g per day is devoid of stimulant action.) Our initial trial of DMAE in schizophrenic patients was at a dose level of 250 mg per day. These patients showed increased motor and verbal activity and insomnia. After 4 weeks the daily dose was reduced to 50 mg per day because of weight loss in the 12 male patients (average 5-lb loss), although urine and blood studies disclosed no abnormality. Since then, 40 to 50 patients have been on therapy for 1 year, during which time the laboratory findings have been within normal limits (*13*). The possible beneficial effect of DMAE therapy in the chronic schizophrenic patient is a gradual one and requires 6 months or more of therapy. We postulate that DMAE therapy can be made more effective in the chronic schizophrenic when biochemical adjuvants are found which will increase acetylcholine synthesis.

In patients other than schizophrenic, DMAE produces relief of periodic headache, functional bowel distress, and chronic fatigue syndromes. DMAE therapy has not made asthmatic patients worse and has not precipitated peptic ulcer symptoms but has slightly increased the incidence of grand mal seizures in two epileptic patients. The incidence of petit mal seizures is, in contrast, diminished by DMAE therapy. The central nervous system stimulation which occurs in man is not accompanied by a rise in blood pressure, a rise in body temperature, or a change in the plasma level of protein-bound iodine. Pharmacological and biochemical studies designed to elucidate the exact mechanisms of action of DMAE are now in progress.

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Evidence that Glutamine Is a Precursor of Asparagine in a Human Cell in Tissue Culture

Previous work from this laboratory (*1–3*) has shown that glutamine is required for the growth of a wide variety of mammalian cells in tissue culture and that, in the case of the HeLa strain human carcinoma cell, it is utilized for protein synthesis without prior degradation. This conclusion was based in part on the observation that, when the cells were grown on a medium containing L-glutamine labeled with C^{14} in the carbon chain and N^{15} in the amide N, the glutaminyl residues of the protein had the same ratio of C^{14} to N^{15} as did the glutamine in the medium. Aside from the amide N of glutamine, the only constituent of the cell protein which contained appreciable N^{15} under these conditions was the amide N of asparagine (*2*) (Table 1). Unlike glutamine, asparagine was not an essential nutrient for these cells, and the close parallel between their N^{15} contents suggested the possibility that glutamine amide N might be a precursor of the asparagine of the protein. However, since the glutamine in the medium was degraded to glutamic acid and ammonia during the culture of the cells (*2*), these data offered no way of deciding whether the pathway between glutamine and asparagine proceeded by way of free ammonia.

Table 1. N^{15} content of the amide groups of the glutamine and asparagine of HeLa cell protein. The N^{15} content of the isolated amide N is referred to that of the precursor as 1. The values are corrected for the amount of protein present at the start of the experiment. The starting glutamine in various experiments contained from 2 to 8 atoms percent excess N^{15}; the NH_4Cl contained 20 atoms percent excess N^{15} in each instance. The conditions of cell growth, the determination of N^{15}, and the isolation of the glutamine and asparagine amide N from enzymatic hydrolyzates of protein by means of glutaminase and asparaginase have been described (*3*).

Precursor in medium	Expt. No.	Relative atoms percent excess in the isolated amide N	
		Glutamine	Asparagine
L-glutamine amide-N^{15}	1	1.2	1.2
	2	1.1	0.82
	3	1.1	0.86
	4	1.1	0.86
$N^{15}H_4Cl$	5	0.012	0.008
	6	0.012	0.008
	7	0.008	
	8	0.008	

If the incorporation of N^{15} into the amide group asparagine does involve ammonia as an intermediate, then culture of the cells in a medium containing $N^{15}H_4Cl$ should lead to labeled asparagine, provided that the ammonia in the medium is available to the cell for biosynthetic processes. Salzman in this laboratory has, in fact, shown (*4*) that when HeLa cells are grown with $N^{15}H_4Cl$, the intracellular soluble pool of ammonia is heavily labeled with N^{15}. Consequently, the data in Table 1, indicating that $N^{15}H_4Cl$ in the medium is not incorporated into the asparagine of the protein to any significant extent, indicate that free ammonia is not an intermediate between glutamine and asparagine. At least, if the transfer of the amide nitrogen of glutamine to asparagine does involve ammonia, then this ammonia is

not in equilibrium with the intracellular metabolite pool.

Free asparagine has been demonstrated in mammalian tissues (*5*) and plasma (*6*), and it appears to be a regular constituent of proteins (*7*). Ohno has recently shown (*8*) that lysozyme has 12 asparaginyl residues and only one aspartyl residue. Despite the wide occurrence of asparagine, little is known of its biosynthesis. Mardashev and Lestrovaya (*9*), on the basis of experiments with rat liver slices, proposed a transamidation between glutamine and aspartic acid yielding asparagine and glutamic acid, but there is as yet no unequivocal evidence for the proposed reaction. It should be emphasized that the results described in this report offer no clue to the mechanism of transfer of the amide group or to the nature of possible intermediates. They do, however, render it unlikely that asparagine is formed in this system by the direct amidation of aspartic acid by ammonia (*10*).

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Acquisition of Resistance to Osteolathyrism during Adaptation to Cold

"Crossed resistance" is a condition in which exposure to one agent induces resistance to another agent (*1*). Analysis has shown that, in most instances, this phenomenon is due to the fact that the stress of exposure to a noxious agent results in a discharge of glucocorticoids which, in their turn, inhibit responsiveness to other agents. It has been shown, for example, that through this mechanism, exposure to stressors (cold, muscular exercise, trauma, and infections) can inhibit the lung edema normally produced by adrenaline, the anaphylactoid reaction usually elicited by egg white or dextran, and many other types of inflammatory responses (*2*).

Since the thyroid also participates in certain systemic adaptive reactions, it seemed of interest to determine whether an increased endogenous secretion of thyroid hormone could likewise produce a phenomenon of "crossed resistance."

Experimental osteolathyrism is a disease characterized by excessive proliferation and degeneration of bone and junction-cartilage tissue (not to be confused with the clinical lathyrism, which affects the nervous tissue selectively). This skeletal disease, which is usually induced in the rat by treatment with *Lathyrus odoratus* or aminoacetonitrile (AAN), can readily be prevented by thyroxin (*3*). It is well known, furthermore, that exposure to cold augments the secretion of thyroid hormone. Could this stimulation of the thyroid during adaptation to a low temperature afford protection against intoxication with aminoacetonitrile?

Thirty female Sprague-Dawley rats with a mean initial body weight of 97 g (range 90 to 107 g) were subdivided into three equal groups. Group I was kept at room temperature throughout the experiment. Group II was kept at 0°C during treatment with aminoacetonitrile and group III was kept at 0°C for 10 days before and during aminoacetonitrile treatment. Aminoacetonitrile hydrosulfate was administered to all three groups, by stomach tube, at the daily dose level of 12 mg (6 mg in 0.2 ml of water twice daily). The experiment was terminated after 16 days of aminoacetonitrile treatment. At autopsy the skeleton was examined macroscopically, and one femur of each animal was fixed and simultaneously decalcified in Susa solution for the subsequent histologic examination of paraffin-imbedded sections stained with hematoxylin-eosin.

Mere macroscopic inspection of the bones sufficed to show that all the control animals (group I) had developed severe osteolathyrism, with multiple exostoses at tendon-insertion sites and excessive periosteal bone formation. Only traces of such changes were seen in group II, and none were seen in group III (Fig. 1). Histologic examination of the bones merely confirmed the macroscopic findings.

The histologic structure of the thyroid was essentially normal in group I, while in the two groups exposed to cold, the thyroid showed cellular hypertrophy and hyperplasia.

Since thyroidectomized rats do not withstand exposure to cold, it was impossible to verify the importance of the thyroid gland in the development of this kind of "crossed resistance" by control experiments on thyroidectomized animals. However, we know that small doses of thyroxin can inhibit osteolathyrism, and exposure to cold did, in fact, cause thyroid stimulation under our experimental conditions. Therefore, it appears justifiable to conclude that the resistance to osteolathyrism, which develops during adaptation to cold, is probably the result of an increased secretion of thyroid hormone.

Fig. 1. Femur of AAN-treated rat kept at room temperature (group I) (left) and femur of a rat which had been kept in a refrigerated room during AAN administration (group II) (right). There is intense bone proliferation (especially in the upper two-thirds of the femur) and widening of the junction-cartilage line (in the distal extremity of the bone) under the influence of AAN at room temperature. These changes are inhibited in the rat that had been kept in the cold.

These experiments furnish us with still another example of an experimental disease whose development is decisively influenced by a hormone. They show, furthermore, that the amount and type of hormone normally secreted by the thyroid during adaptation to cold suffices to induce resistance against a severe experimental malady (*4*).

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Thorium Content of Stone Meteorites

The abundance and distribution of thorium in many terrestrial rocks and in meteorites have not been well defined, owing to the difficulty of detecting the small amounts of thorium involved, compounded with the problem of contamination by extraneous thorium at such low