Nervous Affections.—Neuralgia has been defined as "the cry of a hungry nerve." The pain may be associated with the trifacial, gastric, hepatic, intestinal, or other nerves, and the neuralgia may be designated accordingly. If traumatic irritation has been excluded as an exciting cause of the condition, it is of importance to determine the degree of nutritional failure that is likely to be present in a particular instance. The intimate causal relationship between nerve pains and lithæmia or uricacidæmia, would lead one to endeavor to determine how far an excess of foods containing uric acid is concerned in the production of the neuralgia. Indeed, it would seem justifiable to regard neuralgia as a symptom; it may be of anæmic, lithæmic, gouty, rheumatic, or dyspeptic conditions, and these each, in turn, may be regarded as the products of faulty nutrition. Therefore the principles underlying the dietetic treatment of one condition will apply to all.

First, the habits of the individual must be studied. The food he has been accustomed to take, the care exercised in its preparation, the regularity in eating, and the suitability of the quantity and kind of food to the life work of the individual must be ascertained. A good practice in these, and in similar cases, is to have the patient continue, under observation, for a time without any dietetic restraint. Let a record of each meal be made and submitted for inspection, and in this way it is often possible to discover a potent factor in the causation of a morbid condition. It is well, however, to guard lest a patient in moderate circumstances should bring a list of fare so sumptuous as at once to disprove its accuracy.

The study of the urine, with special reference to the amount of uric acid being excreted, will yield most valuable data regarding the advisability of withholding certain albuminous foods. One cannot study Haig's work on this subject without being impressed with the intimate relationship existing between an excess of uric acid and certain neuralgic manifestations. Indeed, it is hardly possible to determine how far gout, rheumatism, and calculous diseases in general are dependent upon this same condition of uricacidæmia.

That diet is a potent factor in the successful treatment of all these processes is universally accepted. Therefore it is in order to consider what foods will give us sufficient of the various elements necessary for nutrition, and at the same time leave no excess of uric acid in the circulating blood.

The gradual withdrawal of all forms of meat from the dietary, with a proportionate increase of milk, cheese, and gluten foods to supply the nitrogenous food required, and a corresponding increase in the starches, nuts, and fruits, is recommended. No better example of this plan can be given than is found in the tables suggested by Haig (Tables 1, 2, and 3 on page 460).

It is not to be inferred that the dietary is to be limited to the articles suggested in these tables. Indeed, it is surprising to note what a variety of meals can be prepared without meat and the forbidden foods. On the other hand, certain patients find it entirely impracticable to live upon this or a strictly vegetable dietary. In these instances the liberal administration of beef in the form of nutritive beef-tea and scraped or chopped meat cakes, in conjunction with a decided increase in the fats, will give the best results. The fats suitable are obtained in cream, butter, bacon, and in the yolks of eggs, in the form least likely to tax digestion and excite repugnance.

When all the exciting causes of the disease under consideration are eliminated, the diet which maintains a condition of nutritional equilibrium will be the one best suited to the case.

Neurasthenia requires an excess of easily assimilable, highly nutritious food, administered at frequent intervals, in the largest possible quantities. This particularly applies to those cases undergoing what is usually designated "the rest cure." Here the food is urged upon the patient regardless of his desires, and even despite a positive disinclination for food. Milk, cream, and other forms of fat and oils, gruels and easily digested starches, are administered at frequent stated intervals, and the patient is aided in utilizing a part of this nutriment by the administration of massage and electricity, while he stores the remainder in the form of fat and muscular tissue. Indeed, the entire plan of the treatment aims to secure a marked increase in body weight. This is in accord with the view expressed by S. Weir Mitchell, who states that "loss of fat is constantly associated with impoverished blood, and that to gain in fat is nearly always to gain in blood." Many cases of neurasthenia which do not undergo the rest cure are greatly benefited by an ocean voyage, where there is usually a condition of limited expenditure of mental and muscular effort, coupled with an inclination to ingest and ability to digest excessive quantities of food. A neurasthenic who travels for his health should not be allowed to consume, in long journeys, irregular meals, and hasty sightseeing, all the energy developed from his ability to take increased quantities of food.

Insomnia is frequently referable to one or two classes of causes:

(*a*) Improper eating or drinking before retiring.
(*b*) Deficient nutrition.

The patients of the first class require only to have the food, drug, or drink that has been causing the insomnia to be cut off, and to have the evening meal composed of easily digested food. This, with the temporary use of a hypnotic, should accomplish a cure.

In the second class of cases an effort should be made to place the patient upon a higher nutritive level by the administration of light nourishing food between meals, and a cup of hot milk, a milk punch, or malt beverage with a biscuit before retiring. A complete food, such as "Bartholow's food," taken before retiring, will frequently insure a night's repose. It is desirable to have some milk or crackers at the bedside, in case they should be required during the night. The objection to liquors and malt beverages, as an aid in inducing sleep, does not apply to this class of cases as it does to the cases of insomnia occurring in youth.

Epilepsy is so rare in the herbivora, and so frequent in the carnivora that the immunity of the vegetarian animals would seem to give us a positive dietetic indication for the treatment of this disease. The red meats and coarser forms, such as bologna, seem to be especially prone to excite convulsive attacks. Gorging with food, especially improperly masticated meats and other forms of nourishment—notably peanuts—are noted as being likely to excite epileptic paroxysms.

The intimate relationship between the ingestion of an excess of unsuitable and improperly masticated food and an epileptic seizure must be familiar to all those who have given considerable attention to this class of cases. The dietetic treatment of epilepsy promises most when the patient is under the complete control of an attendant. For this reason the epileptic colonies should secure the best results, other things being equal.

The diet that promises most for these cases is one in which meat is reduced to the lowest quantity consistent with the demand for work and growth. In early youth and old age, fish and white meat, with the occasional administration of red meat for the noon meal, are best. Aside from this, the diet should consist of cereals and vegetables, and the meals should be eaten at fixed hours. The frequency of the attacks during the night would suggest the desirability of having the evening meal composed of easily digested food.

Exanthematous Diseases.—The diseases characterized by a skin eruption in the course of an acute febrile process will demand especial dietetic direction only in those instances in which nephritis has occurred as a complication. Here milk is to be made the exclusive nourishment, until the absence of albumin from the urine indicates the improved condition of the kidneys and permits a more extended dietary.

Skin Diseases.—These, when not of parasitic origin, are frequently influenced by diet. The causal relationship between the occurrence of urticaria and the eating of

certain fish, molluscs, fruits, or cereals is fully established. Certain cases of eczema, acne, psoriasis, furunculosis, dermatitis, and pruritus can be favorably influenced by attention to the character and quantity of the food. That there is found associated with indigestion and lithæmic states a condition favoring the development of skin eruptions, there can hardly be any reasonable doubt. The diet outlined for lithæmia will be found suitable for these cases (*vide* section on Gout).

B. Franklin Stahl.

DI-ETHYL-KETONE.—$(C_2H_5)_2CO$, metacetone or propione-ethyl propionyl. This is a colorless, mobile liquid obtained by the dry distillation of sugar with an excess of lime. It smells like acetone, boils at 101° C., and is soluble in twenty-four parts of water, and freely in alcohol and ether. Well diluted, it has been administered by Giovanni in doses of from 0.5 to 1.5 gm. (gr. viij.–xxiv.) to control maniacal or hysterical excitement, and by Albanese and Barabini to induce sleep in animals.

W. A. Bastedo.

DIFFERENTIATION.—(Med. L. *differentiare*, from *differentia*, difference.) Murray defines *differentiation* as "any change by which like things become unlike, or something homogeneous becomes heterogeneous." In the more special, biological, use of the term it is employed to indicate "the process, or the result of the process, by which in the course of growth or development a part, organ, etc., is modified into a special form, or for a special function; specialization; also the gradual production of differences between the descendants of the same ancestral types." In its biological meaning, then, the term may be applied either (1) to certain phenomena in the development of the individual, or (2) to the origin of species; and in each case it may be used to indicate either (*a*) the process, or (*b*) the result of the process.

Taking these meanings in the reverse order, the result, or state, of differentiation of species (2, *b*) would be exhibited by a comparison of the various organs, tissues, habits, modes of life, and other characters of the numerous species and other groups of both animals and plants. It would involve not only a study of their comparative anatomy, but also of their physiology and ecology as well; and thus would be far beyond the scope of the present article.

For the differentiation of species regarded as a process (2, *a*) the term *organic evolution* is commonly employed, and the subject will be discussed in the present work under that title (see article *Evolution*).

In the individual, as among species, the state of structural differentiation (1, *b*) is inseparably associated with functional differentiation, or division of labor. In order to describe the state of differentiation in any form of animal or plant, it would be necessary to make an extended study of the structure of its various organs and tissues and of the various functions that these parts perform in the economy of the whole. For man the results of such studies are set forth in the books upon descriptive anatomy, histology, and human physiology.

The *process* of differentiation by means of which differences arise in the structure and functions of parts of the organism (1, *a*) may be considered under two headings. First, we have the facts in regard to the processes that have been observed in the study of the development of organisms; and, second, we have the theories that have been advanced to explain these facts.

In no existing form of life is there an entire absence of the state of differentiation in any stage of development of the individual. In the protoplasm of the amœba one may distinguish endosarc and ectosarc, nucleus, and contractile vacuole. The protoplasm of bacteria was supposed for a long time to be homogeneous; but Bütschli has demonstrated that by proper methods of staining two distinct substances may be observed. In the germ cells of all the higher animals and plants it is always possible to distinguish nucleus and cytoplasm. In the ova of many animals the cytoplasm is differentiated into two parts: one which contains nutrient material in the form of yolk granules, and the other which is free from yolk, and in which the process of development begins;—not to mention various differentiations in minute structure which cannot be entered into here. The ovum, however, is vastly less differentiated than the adult form, even in the simplest of multicellular organisms.

The process by which the differentiated condition of the adult arises is essentially a cellular phenomenon. In general, development may be divided into three stages: first, cell division; second, growth by the absorption of water and other material; and, third, differentiation. These stages are shown in their simplest forms in the growing ends of the roots or stems of plants. At the tip there is a group of small cells with thin walls and relatively dense protoplasm, in which the nuclei may be seen to be in various stages of cell division. Separated from these by cells in various intermediate stages, there is a zone of cells still having thin walls, but which are much elongated and have numerous large vacuoles in the cytoplasm. In this zone cell division is comparatively rare. It is the zone of growth, and on its proximal side grades off into the next zone, where cell division entirely ceases, the cell walls become thickened, and the cells become differentiated into epithelium, bast, wood fibre, ducts, etc.

In animals the process is not so simple, nor is it always so in plants; for in reality there are two forms of differentiation occurring more or less at the same time. One we may call *anatomical differentiation*, and the other, *histological differentiation*.

During the periods of cell division and growth the cells do not all divide with equal frequency, nor do they all enlarge to the same extent. When the cells tend to arrange themselves in layers, as they do in animals, this inequality of growth causes foldings, the folds may fuse together, and old connections may dissolve. In this way unequal division and growth of the cells, resulting in folding, fusions, and separations, cause a differentiation of the mass of the ovum, whereby the areas are determined which shall include the rudiments of the various organs. In the embryo chick, for example, one may see the boundaries of the central nervous system, the notochord, the heart, etc., while the cells composing these rudiments are still in the most embryonic condition and cell division is going on rapidly. Thus, anatomical differentiation begins in very early stages of development, and precedes the process of histological differentiation, which results in the modification of the cells so that they may form the tissues appropriate to the organs or parts of organs in which they lie. (Further details in regard to the facts of differentiation may be found in the articles *Area Embryonalis*, *Fœtus*, *Gastrula*, *Germ Layers*, *Segmentation of the Body*, etc.)

When we come to consider the conditions under which individual differentiation takes place, we see at once that these may be divided into two categories. For example, we may take an egg of a sea urchin and an egg of a starfish, small transparent eggs not very different in size or general appearance and yet sufficiently unlike to be easily recognized. These, placed together in a bowl of clean sea water of the necessary temperature, and containing sufficient oxygen, will proceed to develop into larvæ; and, although the conditions of the environment are exactly alike for both eggs, one will become the larva of a sea urchin and the other the larva of a star-fish, according to the source of the egg. Or, again, consider a new-born litter of puppies. They are out of the same bitch, have been sired by the same dog, have undergone development at the same time in the same uterus. Yet these puppies will be sufficiently different so that each one may be recognized easily. On the other hand, any puppy in this litter will resemble the others and both parents more closely than will any puppy out of a similar litter dropped by any other bitch and sired by another dog. It is evident that there is something inherent in the germ cell that causes differentiation to proceed in a certain way more or less independently of surrounding conditions. Moreover, the resulting peculiarities of the offspring are correlated with the peculiarities of the parents at the corresponding stages of development; but the correlation is not perfect.

That the course of differentiation is not entirely independent of external conditions, but, on the contrary, is strongly influenced by them, may be shown by a number of experiments. For example, take seeds of two kinds of plants, say a bean and a petunia, and plant them side by side under the same conditions of soil, temperature, and moisture, and exclude all light. The seedlings will develop with long, slender stems, and small, yellow leaves. Seedlings of the same plants grown in full sunlight, other conditions being the same, will have shorter and thicker stems, and larger dark-green leaves. Here we see that seedlings of two kinds of plant have certain characteristics in common which are correlated with the presence or absence of light while differentiation is in progress. Nevertheless in each case one plant is always a bean and the other a petunia, according to the seed from which it has arisen.

We see, then, that differentiation is influenced by two sets of factors,—an internal and an external. The correlation between parent and offspring that is associated with the *internal* factor is what is ordinarily meant by heredity, and as various theories of heredity involve a consideration of the internal factors of differentiation, they will be most conveniently discussed under that title (see article *Heredity*).

The study of the *external* factors which affect the course of growth and differentiation is a new branch of biological science, called experimental morphology, developmental mechanics, or the physiology of development. Investigation in this line has only just begun, and therefore but little is known in regard to the influence of the external conditions and as to their importance relatively to the internal factors. Enough is known, however, to show that their importance is very great.

A few experiments may be mentioned to illustrate the methods that have been employed in attempts to solve this problem. The experiments will be classified according to the external condition that has been investigated.

Gravity.—A number of experiments have been made which show that in some animals the planes of cleavage in the early stages of the division of the egg are determined by the direction of the force of gravity. For example, Pflüger found that if the egg of a frog be fixed so as to prevent rotation, the first two cleavage planes would be vertical in whatever position the egg might be placed, and the third cleavage is generally at right angles to these and nearer the pole of the egg which is held uppermost. In order to obtain perfect embryos, however, it is necessary to have some part of the black hemisphere on the upper side.

It is impossible, of course, to increase the force of gravity. But the same effect may be obtained by placing an object in a centrifugal machine. Hertwig found that by rotating frog's eggs in a centrifugal machine he was able to change the style of cleavage from a holoblastic to a more or less mesoblastic type (see article *Segmentation of the Egg*), so that at the end of twenty-four hours the egg would resemble a hen's egg in having a blastoderm consisting of small cells enclosing a blastocœl and a large undivided yolk containing a few nuclei which lie close under the blastoderm.

Loeb found that the direction of gravity is a factor in determining the differentiation of parts in certain hydroids. Thus, part of a stem of Antennularia being suspended in its normal position in sea water, a new stem will grow out from the upper end and new stolons will appear at the lower end. But let the position be reversed. Then the base, which is now uppermost, will produce the new stem, and stolons will grow from the apex, which is pointing downward. The effect of gravity is still further shown by placing a piece of the hydroid in a horizontal position. Then the ends of the lateral branches on the lower side grow out in the form of stolons, while new stems appear on the upper side.

Contact.—Contact with foreign bodies has been found to influence the differentiation of tissues in the hydroids.

Experimenting with Margeliss and Pennaria, Loeb found that parts of the stem in contact with the glass of the aquarium, even the apical end, would produce stolons; while all parts freely surrounded by sea water would produce hydranths. Similarly, Miss Peebles discovered that pieces of the stalk of Hydractinia and Podocoryne form stolons instead of hydranths if left undisturbed in contact with some hard substance.

When the cut surfaces of hydroid stems, either of the same individual, or of different individuals of the same species, or of different species, are held in contact, they may unite and form a graft, as in plants; and Crampton has shown that the same thing may be done with the pupæ of moths.

Stress and Strain.—Mürthle has shown that a certain amount of pressure and strain is necessary for the proper development of bone. Hermann von Meyer and Culmann discovered that the lamellæ in the spongy portions of the long bones of mammals are arranged with definite relation to the direction of the stresses to which the bones are normally subjected; and Julius Wolff found that, when the direction of stress is changed as the result of dislocation or disease, the lamellæ that are no longer in the lines of pressure or strain will dwindle and new ones will be formed in the positions where they are needed.

Light.—On the higher green plants prolonged darkness induces abnormal growth. The stems are not only greatly elongated, but the supporting tissues are imperfectly developed, so that the stems are soft and tender. The leaves are small and narrow and not fully extended. Even partial shading may result in alteration of the histological structure of leaves, as Stahl found from the study of the leaves of beech trees. A leaf that is fully exposed to the sunlight has under the epidermis on the upper side a layer of very high and narrow palisade cells closely packed together; below this there are one or two layers of similar cells, and the lower third of the leaf is occupied by a rather compact spongy parenchyma. In a leaf that has grown in deep shade, on the other hand, there is but a single layer of short conical palisade cells separated by wide interstitial spaces; and more than half the thickness of the leaf is due to a layer of loosely connected star-shaped parenchyma cells. Between these two extremes various intermediate grades may be found according to the amount of light received by the leaf.

There is not much known about the effect of light upon differentiation in animals; but Poulton found that the color of the pupæ of certain butterflies depends upon the amount of light reflected from surrounding objects at the time that the caterpillar becomes fixed; and Loeb and Miss Peebles found that the presence or absence of light has a certain amount of effect upon the regeneration of the hydranths upon the cut stems of hydroids.

Temperature.—That heat has a marked effect upon the rate of growth is well known, but little has been ascertained as to what effect it may have upon differentiation. We have, however, the interesting experiments of Weismann and of Edwards, who have shown that in several species of butterflies, where there are several broods in the course of the year with different markings, the differences of color depend upon the temperature to which the pupa has been subjected.

Chemical.—For normal development a normal chemical environment is of the greatest importance. A mere trace of some substance may be all that is necessary for normal development that will not occur in its absence. And, on the other hand, the presence of some substance not normally present may so disarrange the processes of development as materially to alter the character of the organism. Thus a trace of a soluble iron salt is necessary for the development of a green plant. Without it, not only is the green coloring matter absent, but the protoplasmic chlorophyll bodies also fail to appear. Knop experimented with Indian corn, treating it with sulphite of magnesium, and he obtained plants so modified that they had lost the distinctive characters of the genus Zea.

Wagner, Gies, and Kassowitz, by feeding young animals with minute doses of phosphorus (0.0015 gm.) and arsenic (0.0005 to 0.001 gm.), produced striking alterations in the formations of the bones. The normal fusion of the cartilage with the young bone was hindered, and in the epiphyses, instead of spongy bone, there was produced a very peculiar compact bone. In the shafts of the long bones the formation of the medullary space was hindered so that the walls of the bone became very thick and heavy.

The Pluteus larva of a sea urchin is normally provided with eight arms, which carry a band of cilia and serve as locomotor organs, and these arms are supported by a calcareous skeleton. Herbst found that a trace of potassium nitrate added to the sea water in which the larvæ are reared will prevent the formation of both skeleton and arms. Pouchet and Chabry obtained the same result by the more obvious method of rearing the larvæ in sea water from which the calcium salts had been removed. Of course, in this case the skeleton could not form from lack of material, but it is interesting to note that where the skeleton failed the arms failed also.

Another and more remarkable modification of the Pluteus was obtained by Herbst by adding a trace of lithium chloride to the sea water. In this case, the so-called lithium larva, the endoderm turned outward, instead of being invaginated in the normal way. Loeb obtained the same result by simply diluting the sea water, which would seem to indicate that the action of the lithium salt in some way interferes with the normal osmotic properties of the cells.

Finally we may mention the remarkable experiments made many years ago by Schmankewitsch upon Artemia, a small crustacean inhabiting the brine of salt works. By rearing these creatures for a number of generations in water of different degrees of salinity he was able to obtain diverse forms which had been regarded formerly as three distinct species, and one of them had been given a separate generic name.

Mixed Conditions.—There are cases in which it can be shown that change of environment induces a change in the organism, but the nature of the former change is so complex that the exact factors cannot be determined. For example, aquatic plants have certain characteristics of structure that distinguish them at once from land plants. Now there are certain plants that live with their stems partly in water and partly in air. In such plants the submerged portions have the character of aquatic plants, while the aerial portions have that of land plants. Here it is impossible to tell how much of the difference is due to the chemical or mechanical effect of the water, the freer access of oxygen, differences in light, temperature, etc.

Food.—Finally, it should be noted that the relative abundance of food has been shown in some cases to have an effect upon the differentiation of sex (see article *Sex*).

These experiments taken as a whole are of great interest because they make it evident that external conditions play a very important part in the normal differentiation of organisms, and they give us some idea, although a very imperfect one, as to what these conditions are and as to how they act. Little progress has been made in experimentation in this direction upon the higher mammals; but we do know that in these forms the presence of certain internal secretions, such as those derived from the thyroid gland, the suprarenal bodies, and the testes, are necessary in the later stages of development in order that normal differentiation may take place; and we may infer that the various factors, such as gravity, pressure, contact, light, heat, and various chemical substances, which have been found in the lower animals and plants to aid or to hinder the normal course of differentiation, may have a similar influence upon the life history of the higher mammals, mankind included.

Robert Payne Bigelow.

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DIGESTANTS are defined as "remedies that aid digestion." The purposes of this article will probably be best subserved if in treating the subject we keep close to the terms of the definition, for it might lead us too far afield if we should undertake to discuss all the various appliances or agencies which exert a favorable influence on digestion. For instance, exercise in one form or another distinctly aids digestion; the use of the thyroid extract immensely improves the nutrition of the cretin, or sometimes a brisk emetic, by relieving the stomach of a task that it is unequal to, will presently enable it to resume its proper function; but no one of these three would properly be called a digestant.

The principal remedies, then, that we must consider are those which act in the stomach and intestines, and we shall try to group them according to their supposed action and the faults of digestion they are severally believed to meet.

Bitters form a numerous class, many of which, such as cinchona and its salts, and hydrastis, possess other properties besides their bitterness, which do not concern us here. Among the best known are calumba, quassia, gentian, orange, cinchona, nux vomica (with its alkaloid strychnine), hydrastis, hops, condurango, and salicin. When taken into the mouth they, especially if administered in the form of a tincture, increase the flow of saliva, but their special use is in promoting the appetite or relish for food, which is essential to normal digestion. Consequently it is customary to give them before eating, and they are the efficient ingredients of the various "bitters," technically so called, often used in clubs and barrooms as a fillip to the stomach. The effect of these drugs is increased by various aromatics, as in the case of the compound tincture of cinchona. Strychnine, while acting like the other bitters, is believed to be absorbed chiefly from the intestine.

Carminatives.—In this class belong many spices, such as cinnamon, cloves, ginger, cardamom, also black pepper and capsicum, mint, anise, with hydrocyanic acid, chloroform and its preparations. All of these have a decidedly aromatic flavor with, in some instances, a sharp or stinging taste. Many of them have long been used as domestic remedies in the shape of teas, in which the hot water probably did the most good, while the aromatic flavor made it possible to take and retain a large quantity. The ingestion of them is usually followed by eructations of gas. They are used in cases of flatulent distention without inflammation and when there is no marked irritation of the stomach and bowels.

Alcoholics include the different wines in common use, spirits such as whiskey, brandy, and gin, as well as those strongly alcoholic and aromatic syrups called cordials, among which are curaçao, maraschino, Kümmel, and others. They are most widely recognized and popularly used both as direct aids to digestion when it is not seriously at fault and as a ready help in time of great trouble from conditions similar to those in which carminatives are indicated. Their heating and stimulating properties on such occasions relax the spasmodic contraction of the muscular fibres of the intestinal walls so that regular peristaltic movements can again take place, the painful distention is removed and the confined gases are dispersed or expelled. The value of small quantities of diluted alcoholics in promoting or diminishing the activity of digestive processes, especially in the stomach, is not yet apparently definitely determined, and probably varies according to individual conditions or peculiarities, for the observations and experiments of physiologists of equally good standing are mutually contradictory (Cushny).

Cathartics certainly come within the terms of our definition, for imperfect and irregular action of the bowels is one of the most fertile causes leading to indigestion, albeit the ways in which cathartics act as aids to digestion are various and often remote. Their number is so