with an artificial reproduction of its native climate. On the other hand, many natives of the tropics find no difficulty in living in the colder temperate zones. Parrots introduced into England flourish in the woods of Norfolk, and that they have not spread over the island is more a matter of food supply than of inimical climatic conditions. The tiger stands the jungle climates of Bengal and the snows of Thibet with equal impunity. The elephant, found now only in the tropics, once roamed over the tablelands of Siberia. The matter of food supply and the ease with which food can be obtained are more influential than the direct physiological effects of the climate itself.

Adaptation to climatic conditions is seen in many animals. The change of color and of thickness of the pelage with the change of seasons is a physiological tribute to climate. The peculiar body formation of many animals is an accommodation to the direct influence of climate. The arboreal animals are unfitted for the treeless prairie. The camel is found in the desert, but it would perish in the forest. Sheep and goats are adapted to the climate of mountains, but not to that of forests. In each and every case we shall find an effort at accommodation in one way or another to climatic environment, and in most of the cases the adaptation is one rather to the food supply, and ultimately to the vegetation of the climate, than to the immediate physiological effects of the meteorological environment.

The key to climatic control of the distribution of animals is in the struggle for food. Many of the extinct animals disappeared not from any secular change of climate, but simply from the advent, often perhaps accidental, of some other form that preyed upon it or its food supply. Goats introduced into the island of St. Helena destroyed a whole flora of trees, and with it doubtless disappeared many if not all of the parasites dependent upon it. Swine introduced in Mauritius destroyed the dodo. The mongoose in Jamaica has completely exterminated the native fauna of this island.

Climate and Vegetation.—The character and distribution of vegetation are both distinctively climatic results. Light, heat, and moisture, in greater or less degrees, are essential to the development of vegetable life. The measures in which these elements are combined determine the general characteristic features of the vegetation. Variations of degree in these characteristics result from the combination of the effects of climate and those of other factors, as the structure and composition of the soil, the effects of animal life, etc. The intense heat and generally abundant moisture of the tropics favor a luxuriant growth in forms that in colder regions are diminutive in size. The vegetation of arid regions is distinct from that of humid countries; and the vegetation of the hot deserts is different from that of the deserts of colder latitudes. Under the equator palms and bananas are the typical forms; then, receding toward the poles, come in succession tree ferns and figs, myrtles and laurels, evergreens, deciduous trees, conifers, lichens and dwarf shrubs, and mosses. If we ascend a high tropical mountain we shall find the same change of vegetational formation.

The following tabular view will present the approximate general distribution of vegetational types with reference to the average temperature under which each best develops.

Zone of—	Average temperature of zone.	Altitude of each under the equator.
Palms, Bananas	82°-70° F.	At sea level.
Tree ferns, Figs	78 -73	From sea level to 2,000 feet.
Myrtles, Laurels	73 -68	From 2,000 to 4,000 feet.
Evergreens	68 -60	From 4,000 to 6,000.
Deciduous Trees	60 -48	From 6,000 to 8,000 feet,
Conifers (pines, etc)	48 -40	From 8,000 to 10,000 feet.
Lichens, Mosses	40 -32	From 10,000 to 12,000 feet.
	32° and lower.	From 12,000 to 14,000 feet.

The distribution of the temperature and the rainfall are the most important factors in vegetation. And it is the heat of the summer rather than the cold of winter that determines the limit of vegetation. A broad generalization has been made to the effect that the geographical distribution of animals is dependent upon that of the minimum temperatures of winter, and the geographical distribution of the different varieties of plants is dependent upon the maximum temperatures of summer. Observation of the lowest temperatures at which most plants begin to germinate shows that vital action is not evident till the temperature rises to 43° F. This is the first effective temperature. Plant growth takes place only so long as the temperature is at or above this point, and the amount of growth that actually takes place, other conditions being favorable, is estimated by the product of the number of hours by the number of degrees the temperature is above 42° F. This product is called the accumulated temperature, and represents the total effective temperature for plant development. The higher the temperature, up to a certain optimum, varying for different plants, the greater the rate of growth. The study of plant growth and meteorology is receiving the scientific attention that it so well merits. When more progress has been made scientific phenology will be a most important and valuable assistance to mankind.

W. F. R. Phillips.

Brief Bibliography of Most Recent Books, Etc.

Abercromby, Ralph: Weather, 1888.
Angot, Alfred: Traité élémentaire de météorologie, 1899.
Annual Reports of U. S. Weather Bureau, 1891 to date.
Bebber, W. J. van: Hygienische Meteorologie für Aertze und Naturforscher, 1895.
Bartholomew's Physical Atlas. Vol. 3, Atlas of Meteorology, a series of over 400 maps. Edited by Alex. Buchan, 1899.
Cullimore, D. H.: Book of Climates for All Lands, 1890.
Davis, W. M.: Elementary Meteorology, 1898.
Dickson, H. N.: Meteorology, 1893.
Ferrel, William: A Popular Treatise on the Winds, Comprising the General Motions of the Atmosphere, Monsoons, Cyclones, etc., 1893.
Greely, A. W.: American Weather, 1888.
Hann, Julius: Handbuch der Klimatologie, 2 Auflage, 1897.
Moore, J. W.: Meteorology, Practical and Applied, 1894.
Scott, R. H.: Elementary Meteorology.
Solly, S. E.: Medical Climatology, 1897.
Transactions American Climatological Association, 1881 to date.
Waldo, Frank: Elementary Meteorology for High Schools and Colleges, 1896.
Williams, C. Theo.: Aerotherapeutics, 1894.
See also articles on Climate in Encyclopædia Britannica, Johnson's Universal Cyclopædia, Stevenson and Murphy's Hygiene, Park's Practical Hygiene, Allbutt's System of Medicine.

CLIMAX SPRINGS.—Camden County, Missouri.

Post-Office.—Climax. Hotel.

Access.—Viâ Missouri Pacific Railroad to Warsaw, thence 25 miles by stage to springs.

These springs are seven in number, and are located in a rolling, heavily timbered region, with many pleasing landscapes. An analysis of the waters was made in 1882 by Prof. N. W. Wiley, of Purdue University, Indiana, State Chemist.

One United States Gallon Contains:

Solids.	Grains.
Calcium oxide	4.98
Magnesium oxide	1.80
Aluminum oxide (with iron oxide)	5.08
Sulphuric acid	3.60
Carbonic acid	3.92
Sodium	14.00
Potassium	1.20
Iodine, Bromine	14.00
Chlorine	20.40
Loss	3.02
Total	72.00

The waters are remarkable for the quantity of iodine and bromine which they contain. They are somewhat similar to the waters of the celebrated Kreutznach Springs, of Prussia, but are far stronger in these ingredients. Such waters are especially adapted for the treatment of chronic syphilitic and scrofulous affections.

The analysis is obviously incomplete, however, and a new examination should be made. We have been unable to obtain a recent report of these springs. The foregoing account is compiled from Walton's work and from the United States Geological Reports.

James K. Crook.

CLOVER, RED.—The flower heads of *Trifolium pratense* L. (fam. *Leguminosæ*). The herbage of most of the two or three hundred species of *Trifolium* is rich in albuminous nutriment, or *legumin*, and red clover is one of the best and the most extensively cultivated of these fodders. During recent years it has come into prominence as an ingredient of a "shotgun" preparation, used as an alterative of which the other ingredients represent the activity. *Henry H. Rusby.*

CLOVER, SWEET. MELILOT.—The dried herb of two species of *Melilotus*, *M. officinalis* Desr. and *M. altissimus* Thuill. (fam. *Leguminosæ*). These are tall, upright, or straggling biennial herbs, with small trifoliolate leaves and axillary spikes of minute clover-like flowers. Both plants are fragrant, having the pleasant odor of Tonka beans, which is also increased by drying. They contain also the same odorous substance found in Tonka beans, *cumarin* (cumaric anhydride), as well as the related substances, *melilotus oil*, *melilotic acid*, and *cumaric acid*.

Melilot is a mild and pleasant aromatic of no special value in medicine, and is fairly obsolete. The infusion was formerly employed to a considerable extent as an eyewash. Dose indefinite. *W. P. Bolles.*

CLOVERDALE LITHIA SPRINGS.—Cumberland County, Penn.

Post-Office.—Newville.

This artesian mineral-water fountain is located $2\frac{1}{2}$ miles northwest of Newville and 5 miles south of the Doubling Gap White Sulphur Springs. It was discovered in 1865 by a party prospecting for oil. The opening bored through the solid rock to a great depth struck this water vein, which, being released from its subterranean confinement, gushed to the surface at the rate of three hundred gallons per hour under the pressure of its own carbonic acid gas. The flow since that time has never diminished, being uniform at all seasons of the year. The water is perfectly clear and entirely free of organic matter, and has a temperature at the spring of 52° F. The following analysis was made in 1889 by Prof. E. T. Fristoe, of the Columbian University, Washington, D. C.

One United States Gallon Contains:

Solids.	Grains.
Potassium carbonate	0.20
Lithium carbonate	0.17
Magnesium sulphate	1.60
Magnesium chloride	0.09
Sodium chloride	Trace.
Magnesium bicarbonate	0.42
Calcium bicarbonate	6.67
Iron oxide and alumina	0.75
Silica	0.80
Phosphoric acid	Trace.
Total	10.70
Gases.	**Cubic inches.**
Carbonic acid	1.070
Oxygen	1.109
Nitrogen	6.013

This water is not heavily impregnated with mineral ingredients, yet when taken in sufficient quantities it exerts an undoubted influence on the physical economy. It has been found to possess antacid, mild aperient, and tonic effects. Its clear and sparkling appearance and freedom from organic impurities qualify it for table and domestic purposes. It is said to have been found fresh and palatable after three years' bottling. The water is used commercially. *James K. Crook.*

CLOVES.—*Caryophyllus*, U. S. P.: *Caryophyllum*, B. P. "The unexpanded flowers of *Eugenia aromatica* Linn." (U. S. P.). "The dried flower buds of *Eugenia caryophyllata* Thumb." (B. P.). This tree, to which each pharmacopœia has given a different name, is a member of the order *Myrtaceæ*, in which are included many aromatic plants such as the allspice, bay, cajuput, and eucalyptus. It is a beautiful, fragrant, evergreen tree, with a fine pyramidal crown thirty or forty feet high, and with bright crimson flowers. The branches are numerous, slender, horizontal, the leaves opposite, lanceolate, pointed, entire, dark green and shining, and covered with glandular dots. Flowers in terminal clusters, articulated. Calyx brilliant crimson, with a long, solid, flattened, cylindrical tube (receptacle of Baillon), in the

Fig. 1386.—Clove Tree, flowering branch one-third natural size. (Baillon.)

upper part of which the minute ovary is embedded, and four thick, spreading, triangular lobes. Petals also four, cream-colored, orbicular, arched, in the bud imbricated in a perfect globular head; stamens very numerous, ovary minute, two-celled, many-ovuled, embedded in the fleshy calyx mass; style slender, single. Fruit oval, crowned with the four conniving calyx teeth, one-seeded (the mother cloves of the market). Length of flower about 1.5 cm. ($\frac{1}{2}$ in.), of fruit about 2.5 cm. (1 in.).

Its orginal habitat was the Molucca and Philippine Islands, but it is now cultivated in the islands of the Indian ocean, Southern India, Africa, the West Indies, and South America. The buds are collected just before the petals expand and the process requires much care and experience. If gathered too soon, the clove is deficient in its aromatic constituents; if too late, the corolla expands when drying. The buds are dried in the sun, and much attention is given to procure the characteristic rich brown color. All parts of the plant are aromatic, and the small branches are often broken into small pieces and colored for the purpose of adulteration. Ground cloves often are made up of a large proportion of the branches and also of the fruit. Another adulteration of ground cloves is the addition of cloves from which the oil has been abstracted. The clove somewhat resembles a nail in shape, its name being derived from the French *clou*. "It is over half an inch long, dark brown, consisting of a sub-cylindrical, solid, and glandular calyx tube, terminated by four teeth, and surmounted by a globular head, formed by four petals, which cover numerous curved stamens and one style. Cloves emit oil when scratched, and have a strong aromatic odor, and a pungent, spicy taste" (U. S. P.). Cloves contain a large percentage of the official oil, which forms as much as one-fifth of its bulk. There are also present tannin, gum, resin, etc.; *caryophyllin*, $C_{20}H_{32}O_2$, which is isomeric with camphor; and *euginin*, none of which are of any therapeutic value. The properties of the clove are contained in the volatile oil. It is obtained by distillation, and is official in the United States Pharmacopœia and British Pharmacopœia. When first procured, the oil is clear and colorless and very fluid; with age and exposure it becomes yellow in color, and ultimately reddish brown. It also becomes thicker. Its specific gravity should be 1.060 to 1.067 at 15° C. It is heavier than water, soluble in equal volumes of alcohol, ether, and acetic acid. It is slightly acid in reaction. Oil of cloves is made up of *eugenol* (*eugenic acid*), $C_{10}H_{12}O_2$, chemically resembling phenol and guiacol, and a terpene, $C_{15}H_{24}$, which is deposited when the oil is kept for a length of time.

Eugenol is formed by a process of oxidation from oil of cloves, and may also be procured from other essential oils, as those of cinnamon, pimento, sassafras. It is an aromatic, colorless, or brownish, oily liquid, insoluble in water, soluble in alcohol, and forms compounds of a definite character with caustic alkalies. It possesses antiseptic properties, and has been recommended as a febrifuge, but is inferior to salicylic acid, quinine, etc. Eugenol, the action of which is somewhat analogous to guaiacol, was brought into prominence by Dr. Koch, who suggested its administration during the tuberculin treatment. The dose is ♏ xlv. during the day, dissolved in spirit and diluted with water. Applied locally it has a mild anæsthetic action.

Two derivatives of eugenol—benzoyl-eugenol and cinnamyl-eugenol—have been introduced and are advocated for the treatment of tuberculous disease. Both of these preparations occur in neutral, acicular crystals, free from color and odor; taste, faintly bitter; slightly soluble in water and freely soluble in alcohol.

The therapeutic action of cloves is due to the volatile oil which they contain, and is that common to all aromatic oils. Externally it is antiseptic, stimulant, and, when freely used, is a counter-irritant. It also is slightly anæsthetic. It is employed locally only as a remedy for rheumatic pains, sciatica, and neuralgias. Its most common use is as an antiseptic and anæsthetic application to carious teeth.

When taken internally it produces a stimulating and antiseptic effect upon the mucous membrane of the stomach and bowels. It also acts as a carminative and antispasmodic, checking fermentation and promoting digestion.

After absorption it produces a general stimulation and is excreted unchanged by the kidneys, liver, and bronchi. Upon these tissues it exercises its antiseptic properties, and it is thought that this is specially directed to the pulmonary tissues. It is this local action upon the lungs which, with its carminative and stimulating effects, has encouraged its employment in tuberculosis.

The oil is usually selected for administration in from one- to five-drop doses. The dose of powdered cloves is said to be from gr. v. to x. An infusion is official in the British Pharmacopœia, 1 part to 40. Oil of cloves is added to several pills, confections, and other preparations for its carminative effects.

Beaumont Small.

CLUBBED FINGERS; CLUB HAND. See *Hand and Fingers*, etc.

CLUB-FOOT. See *Foot, Deformities of.*

COAGULATION.—Most of the animal proteids can be obtained in solution. Many of these may be coagulated or rendered insoluble by different means. As to the nature of the process, we know very little in addition to the fact that there is a striking difference between the substance formed and the material from which it was produced. The degree of insolubility varies with the different proteids and the means by which coagulation is produced. There is a distinct difference between precipitation and coagulation of proteids. In the former the precipitate may be redissolved again in suitable media, while in the latter the coagulum cannot be dissolved by ordinary media. The difference is well illustrated by the action of alcohol upon proteids. Albumins and globulins are at first precipitated by this reagent—the precipitate may be redissolved; after standing under alcohol for days or weeks they are coagulated and cannot be redissolved. Alcohol also precipitates proteoses and peptones, but does not coagulate them. Ammonium sulphate in saturation will precipitate all proteids except peptones, but does not coagulate any of them.

Coagulation may be brought about: I. By heat or chemical reagents; II. by coagulating ferments or enzymes.

I. Coagulation by Heat.—The coagulation of egg white by boiling is the most familiar example of heat coagulation. The temperature necessary to produce coagulation varies with different proteids. Thus fibrinogen and myosin coagulate at 56° C.; egg albumen and muscle albumen at 73° C.; serum globulin at 75° C. Serum albumin, which was once regarded as a single body, has been found by Halliburton to consist of three different bodies having coagulation points at 73°, 77°, and 84° C. respectively. Not only does the coagulation point vary with different proteids, but even for the same proteid it varies with the salts present and the reaction of the solution. Coagulation occurs much more readily and completely in an acid than in an alkaline or neutral medium.

From the readiness with which albumins and globulins are coagulated by heat they are often called the coagulable proteids.* Vegetable albumins and globulins are coagulated by heat like those of animal origin. Some non-coagulable proteids may be coagulated under certain conditions—*e.g.*, acid and alkali albumins are non-coagulable when in solution, but after precipitation by neutralization they can be coagulated by heat. Proteids coagulated by heat cannot be dissolved by water or saline solution of any strength. Weak acids or alkalies only dissolve them by the aid of heat. The digestive ferments, however, readily act upon them in suitable media.

We know no chemical difference between the coagulum formed by heat and that formed by chemical reagents, but the proteids formed by the coagulating ferments can still be coagulated by heat. Thus myosin of muscle can be extracted by saline solution, but not after it has been boiled. In the digestion of fresh fibrin intermediate products occur which cannot be obtained when it has been boiled. The proteids coagulated by ferments are much more soluble in strong solutions of neutral salts and in weak acids or alkalies than are those coagulated by heat or chemical reagents.

Coagulated proteids behave like native proteids to those tests which can be applied, such as the color tests.

The chemical reagents causing coagulation without definite compounds (such as are formed by salts of the heavy metals) are alcohol, picric acid, tannic acid, and strong mineral acids. Fixation agents such as alcohol, formalin, osmic acid, and mercuric chloride cause coagulation of the proteids of protoplasm in preserving tissues and cause a reticular formation in the cell formerly described as spongioplasm.

II. Coagulation by Ferments.—*A. Coagulation of Blood.*—When blood is shed it soon becomes viscid, and in from three to ten minutes sets in a jelly-like clot or coagulum. The coagulum shrinks and gradually the clear yellowish blood serum separates from the clot. The clot consists of a fibrillar substance, fibrin, entangling the corpuscles in its meshes. Although the clot forms a bulky mass from the large number of corpuscles contained in it, the actual amount of dried fibrin that can be obtained from blood is small, being only from 0.2 to 0.4 per cent. by weight. The corpuscles are not at all necessary for the formation of the clot, as they can be removed in various ways, and coagulation occurs in the fluid of the blood—the plasma—as perfectly as when they are present. The essential part of the clot is the fibrin, a coagulated proteid which is formed when blood or lymph coagulates. The whole problem of coagulation of the blood centres in the formation of fibrin.

* Some nucleo-proteids are also coagulable by heat.

Fibrin is formed from fibrinogen, a globulin which normally is in solution in blood plasma and has certain chemical peculiarities that distinguish it from other globulins. Fibrinogen is completely used up in the formation of fibrin and none appears in blood serum. The amount of fibrin formed is never quite as great as the amount of fibrinogen acted upon. The fibrinogen is split up by fibrin ferment or thrombin, as it is now generally called, into (1) the coagulated proteid fibrin which represents the larger part, and (2) a small amount of a soluble globulin called fibrin-globulin which remains in solution in blood serum.

The thrombin or fibrin ferment does not normally exist in blood but is formed when it is shed. It results from the interaction of a nucleo-proteid with lime salts, and hence this nucleo-proteid has been called prothrombin. Even the nucleo-proteid or prothrombin does not exist in solution in sufficient quantity in the circulating blood to cause coagulation, but arises from the disintegration of blood platelets and leucocytes (especially the polynuclear leucocytes) when the blood leaves the vessels.

Pekelharing supposes that in the cleavage of fibrinogen the thrombin, being a compound of calcium and nucleo-proteid, yields its calcium to combine with a part of the fibrinogen molecule and form the insoluble fibrin; that the calcium-free thrombin (or prothrombin) then again recombines with free lime salts to hand these over in turn in the formation of more fibrin until all the fibrinogen is used up. This is not the case, for different observers have obtained perfect fibrin by adding a solution of thrombin containing no free lime salts to a solution of fibrinogen from which free lime salts had also been removed in the same way—viz., by the presence of soluble oxalates. Further, Hammarsten has failed to find any more calcium in fibrin than in fibrinogen.

It does not follow from this that lime salts are not necessary for coagulation, but only that they do not combine as Pekelharing at first thought, and that they do not play the same part in coagulation of the blood as they do in the coagulation of milk under the influence of rennet (see the section on "Coagulation of Milk").

On the contrary, lime salts are absolutely necessary for coagulation. If the blood be received directly into a solution of a soluble oxalate (such as potassium or ammonium), the *free* lime salts are removed as the insoluble oxalate of calcium, and coagulation cannot take place, although both fibrinogen and the nucleo-proteid or prothrombin are present. The lime salts seem to interact in some way with prothrombin to form thrombin. After the thrombin is once formed the subsequent addition of a soluble oxalate cannot remove any *combined* calcium.

Although nucleo-proteids extracted from various other tissues of the body (lymph glands, thymus, etc.) influence coagulation, none of them behaves like this one (prothrombin) found in the plasma of shed blood. The latter is not coagulated by the prolonged action of alcohol. The most remarkable difference is that thrombin acts upon blood outside the body, but does not act in the same way upon the circulating blood. On the other hand, other nucleo-proteids, if injected into a vein, rapidly cause extensive intravascular clotting, but do not produce extravascular coagulation. This may be due to differences in the nucleo-proteids or, what seems more probable, in the compounds which they form with lime salts.

If the question is asked, Why does the blood not coagulate in the living vessels? it may be answered that neither thrombin nor prothrombin is present in sufficient quantities in the circulating blood to cause coagulation. But if it is considered how difficult it is to produce intravascular coagulation, or thrombosis, as it is called under these circumstances, by the injection of thrombin or fibrin ferment directly into the vein, it will be seen that this answer is not satisfactory. There is no satisfactory explanation of the failure of blood to coagulate if kept in a portion of a vein carefully removed from the body. Neither can we explain why coagulation occurs in the living body when the endothelial lining of a blood-vessel is altered by disease or injured as by a ligature.

The coagulability of the blood varies considerably, and we are unable to explain the cause of it. Thus it is increased in some acute infections such as diphtheria and pneumonia. As there is an increase of the leucocytes, and also of the number destroyed in these conditions, one might suppose it to be due to an increased amount of nucleo-proteid (prothrombin) in the blood plasma. But the coagulability of the blood is also greatly increased in starvation and rapidly increases during severe hemorrhage. In neither is there any leucocytosis, and we are unable to explain the condition, although it seems to be a wise provision of Nature to prevent death from capillary and venous hemorrhage. On the other hand the coagulability may be greatly diminished and, in the curious disease hæmophilia, almost entirely lost. In many of these cases, according to Wright, there appears to be a deficiency of lime salts, and the internal administration or local application of these will stop the hemorrhage.

The liver seems to be concerned in maintaining the coagulability of the blood in some unknown way. Blood that is kept circulating through the lungs and heart alone soon loses its coagulability. If the portal circulation be cut out of the systemic circulation, the blood also loses its property of coagulating, and agents which alter the coagulability of the blood fail to act under these circumstances.

Certain agents can be introduced into the circulation which will increase, or, on the other hand, lessen or completely destroy the coagulability of the blood. Many ingenious theories have been advanced as to the way in which these agents act, but none of them explains the phenomena satisfactorily. The following conditions hasten coagulation: Agitation of blood by stirring or by passing gases; contact with a rough surface. All of these probably act by hastening the disintegration of the cells liberating nucleo-proteid. The presence of CO_2 is favorable, so that the blood in asphyxia coagulates readily. Heat favors coagulation probably by favoring the formation and action of thrombin or fibrin ferment. It is in this way that sponging with very hot solutions stops hemorrhage.

The following conditions retard coagulation: Receiving blood under oil or in a vessel made perfectly smooth by oil or vaseline. If blood be surrounded by a freezing mixture, the cold may delay and even prevent coagulation. If blood be received into a solution of a soluble oxalate of such strength as to form 0.1 per cent., coagulation is entirely prevented because the lime salts have been removed to form the insoluble calcium oxalate. If blood be received into one-fourth its volume of a saturated solution of magnesium sulphate, coagulation is prevented by the neutral salt—probably by preventing the disintegration of cells, as it can be made to clot by adding thrombin. Extracts of the heads of leeches contain some material which prevents coagulation. Commercial "peptone," which is really a mixture of proteoses, will destroy the coagulability of the blood when introduced into the circulation. No satisfactory explanation can be given of this effect.

Certain substances, as nucleo-proteids, albumoses of snake venom, and certain colloidal proteid-like bodies produced synthetically, can be introduced into the body very gradually, and in small quantities they act so as to lessen or destroy the coagulability of the blood—"negative phase" of coagulation. If, however, these same materials are introduced rapidly and in larger quantities, extensive thrombosis ensues in the heart and large vessels and causes instant death—the "positive phase" of coagulation. Although an enormous amount of work has been performed by investigators to ascertain how these remarkable results are produced, no explanation has been advanced that is without some objection.

B. Coagulation of Milk consists in the formation of a curd or coagulum which separates from the clear milk plasma or whey that still holds the salts and milk sugar in solution. The coagulum is composed of the comparatively insoluble proteid casein and the fats of milk entangled with it. True coagulation of milk is brought about by rennin, an enzyme of the gastric juice. Other curdling agents can also act upon milk, but the changes are not the same. The so-called "spontaneous coagulation" or curdling of milk from souring is not true coagulation, but merely the precipitation of caseinogen. If milk is allowed to stand exposed to the air at a warm temperature, the lactic-acid bacillus soon decomposes the lactose or milk sugar with the formation of lactic acid. When this acid reaches a certain amount, it causes a *precipitate* of caseinogen and fat. True coagulation consists in the conversion of caseinogen into the comparatively insoluble proteid casein, but acids do not produce this change.

The action of rennin in changing the soluble proteid caseinogen into the more insoluble casein is not a simple one. The caseinogen is split up into two parts: the comparatively insoluble casein which forms by far the greater part, and a very small amount of a freely soluble proteid resembling a proteose, called "whey proteid" by Hammarsten. This change is comparable to the change which takes place in fibrinogen in clotting of blood. The fibrin ferment acts upon fibrinogen, splitting it up into the coagulated proteid fibrin and a soluble globulin which passes into solution in the blood serum. The coagulation of milk is further analogous to that of blood in that lime salts are absolutely necessary for the chemical changes, and clotting does not occur when they have been removed by dialysis or the addition of a soluble oxalate. The changes, however, are not identical. In the coagulation of blood the lime salts first combine with a nucleo-proteid to form fibrin ferment, and this then acts upon fibrinogen, splitting it up into a soluble and an insoluble proteid. Rennin first acts upon caseinogen, even in the absence of lime salts, to form a "soluble casein," but no curdling occurs. The enzyme may then be destroyed by boiling, but the addition of a lime salt causes coagulation instantly. The lime salt unites with soluble casein to form insoluble casein.

The caseinogen of human milk is different from that of cow's milk, and forms a flocculent curd with rennet instead of a solid mass.

The curdling ferment of the pancreatic juice produces a peculiar kind of casein, called "pancreatic casein" by Halliburton, which is not the same as that formed by rennet. At the body temperature it forms with cow's milk a granular precipitate and not a coherent clot as rennin does. The removal of lime salts only slightly hinders but does not prevent this curdling. The precipitate differs in its solubilities both from caseinogen and casein, and it can still be converted into true casein by rennin.

Extracts of various tissues, as the testis, muscle, and liver, as well as the juice of certain plants, cause curdling of milk probably in much the same way as does this unnamed ferment of the pancreatic juice.

As stated above, the curdling of milk from souring is not true coagulation. This precipitation of caseinogen, carrying the entangled fats with it, can be brought about by other acids, *e.g.*, by the cautious addition of acetic acid. The precipitate resulting from the addition of an acid is usually flocculent and contains less lime than that formed by rennin. It can form even in the absence of lime salts, and is more easily redissolved than is the curd containing true casein. Moreover, it can be dissolved and recurdled by rennin, *i.e.*, converted into true casein. Although true casein can be dissolved, it cannot be recurdled by rennin. This is the most striking difference between caseinogen and casein.

Although the lactic-acid bacillus does not cause true coagulation in the ordinary souring of milk, some bacteria, either by their life activity or by some product of their metabolism, produce a coagulum which appears to be a true clot. This fact is utilized by bacteriologists to distinguish between different kinds of bacteria, but probably occurs only under ordinary conditions in those very exceptional instances when a ropy or stringy clot forms in milk.

C. Coagulation of Muscle.—Rigor mortis, or the rigidity of death, is due to a coagulation of muscle proteids. If the muscles of cold- or warm-blooded animals be freed from blood and mixed with ice and salt, or extracted with a rather strong solution of neutral salt, a clear muscle plasma containing most of the proteids of muscle can be obtained. By raising the temperature in the one case or diluting with water in the other, a coagulum consisting of myosin is formed from the proteids that were in solution and separates from a clear serum. Myosinogen, a globulin-like body which constitutes about eighty per cent. of the proteids of muscle plasma, is converted into myosin. Paramyosinogen, another globulin which is only one-fourth as abundant as myosinogen, is also contained in the clot. Small amounts of other proteids (myoglobulin and myo-albumin) remain in solution in muscle serum. The formation of myosin results from the action of a myosin ferment upon myosinogen. This enzyme can be extracted from muscle in the same way as fibrin ferment is obtained from blood serum. The two, however, are not identical, for fibrin ferment cannot coagulate myosinogen, neither can myosin ferment coagulate fibrinogen. Free lime salts do not appear to be necessary for the formation of myosin. Myosin is much more soluble than other coagulated proteids resulting from the action of enzymes, and is often classed with globulins because of the ease with which it can be dissolved by saline solutions. Further, the difference between myosin and the mother substance from which it is formed (myosinogen) is not so great as in the other cases. In the coagulation of muscle, CO_2 and lactic acid are formed, probably from the chemical changes taking place in the proteids.

The appearance of rigor mortis in the muscles is due to these same chemical changes that have been described in muscle plasma. The rigor often disappears before putrefactive changes appear. A proteolytic ferment has been found in dead muscles, and this is probably greatly aided by the lactic acid in causing the myosin to disappear.

The presence of acids, stopping the blood supply, or heating the muscle will cause coagulation that is often called "acid-" or "heat-rigor." In the cold-blooded frog 40° C., in the mammal a temperature of 48° to 50° C., will cause heat rigor. This is probably only the premature appearance of rigor mortis in the dying muscle. It is entirely different from heat coagulation, as the myosin can be dissolved by solutions of neutral salts, while proteids coagulated by heat cannot. Further, the other chemical changes are the same as in rigor mortis, and the myosin formed is still coagulable by heat.

William S. Carter.

COAGULATION NECROSIS. See *Necrosis*.

COAL GAS. See *Carbon, etc.*

COCA.—*Erythroxylon.* "The leaves of *Erythroxylon Coca* Lamarck" (U. S. P.).

(Owing to their important bearing upon the value and uses of this drug, we find it necessary to discuss in some detail portions of its history which in the case of most drugs are practically unimportant. The several departments are indicated by small capital side-headings, so that the reader can readily refer to any desired portion of the subject.)

DEFINITION.—The limitations of the official definition are by no means clear, though highly important. The different varieties of the coca leaf vary in qualitative action to a degree not recognized in our best text-books and appreciated by very few practitioners. If the one plant is to be regarded as a mere form of the other, then the definition includes two drugs, sufficiently distinct to receive recognition under two titles, as is certainly true of the British Pharmacopœia definition, which says: "The leaves of *Erythroxylon Coca* Lam. and its varieties." If, on the other hand, each is to be regarded as a distinct species, then that leaf which appears to be of the higher medicinal value is excluded from the Pharmacopœia in the interest of one yielding a larger percentage of crystallizable cocaine. There are various good reasons for taking the latter view, so that in this article Coca (U. S. P.) will be regarded as only that variety known as the "Huanuco," or "Bolivian," or "Large Brown" leaf (Fig. 1387). Of this there are noticeable forms or grades, but these may be regarded as differing in degree rather than in kind. Thus, the best Bolivian (Yungas) leaf is rather smaller than the same grown in Peru. The term "Peruvian" is too indefinite for use, as it may reasonably be applied to either this or the Truxillo variety. When we have quite finished with the article thus defined, attention will be given to the Truxillo variety and to other species of the genus.

ORIGIN.—There is no reasonable doubt that the species originated upon the eastern slope of the South American Andes, probably in Peru. Since it was cultivated in prehistoric times, there is no way of certainly ascertaining whether it was wild in its present form or whether the latter is a product of development by cultivation from some other wild form. The latter is probably true, because in the wild (escaped) state it shows a strong and rapid tendency to lose its characteristics. It is impossible to say of any of the wild plants collected by the writer and others that they are not escapes from cultivation, many known to be such having been encountered. Lastly, it is not known whether the ancestral form is one of those still in existence in a wild state.

HISTORY.—The coca plant was under cultivation at the time of the discovery, and no clew to its introduction to cultivation could then be, or has since been, obtained. It occupied an important place in the religious and mythological history of the people. This is of interest here only because of the unquestionable fact that such esteem was the result of an appreciation of its useful properties, rather than, upon the contrary, and as for centuries believed, the superstitious reason for its being used. We may therefore dismiss its mythical history (see "Coca at Home and Abroad," *Ther. Gaz.*, March and May, 1888, also p. 14, 1886) as being here unimportant, and consider its physiological and therapeutical history. Its expectorant, sialagogue, stomachic, carminative, emmenagogue, and aphrodisiac properties are among the minor ones for which it was and is used by the natives. As a stomachic, it is recognized that its use before meals detracts from the appetite, but that its use thereafter relieves any discomfort resulting from excess, while not appreciably inhibiting digestion. In fact, its general repute is that of aiding digestion. The more important objects of its use are as a limited cerebral stimulant, an anæsthetic, a very peculiar muscular stimulant, and an ordinary masticatory. As a cerebral stimulant it filled the place of coffee. It was used before the latter was introduced, and after that event it continued to be used by the natives, while the much more expensive coffee was used by the foreign element. In this direction its characteristics were to promote cheerful and hopeful views and sentiments, without excitability, but rather with increased calm. As an anæsthetic, its use was a general more than a local one, though it was locally applied to ease pain, and its carminative and stomachic uses were clearly of this nature. The object of overcoming the pains of hunger and of fatigue were pre-eminent, while that of securing relief from pain by a mild general anæsthetic, in spite of increased wakefulness, was general.

The term "muscular stimulant" is not accurate, but is used for want of a better. More lengthily stated, the plant was used to enable man to perform more labor with less fatigue and with less nutrition. Without regard to the facts of the case, this was the belief of its users. In consequence of these effects, bodily or mental, they performed almost incredible physical tasks, long-continued, upon a food supply, the scantiness of which is equally astonishing, and with results not injurious beyond causing temporary inconvenience. The special adverse conditions to be met in these efforts were the continued scaling of steep and high acclivities, with little food and with a very scanty supply of oxygen, and under the necessity of either attaining a high speed or transporting heavy loads.

The above statements, in substance, were among the earliest historical records promulgated concerning its use by the people of the countries concerned, and they have been repeated, with assurance, by all subsequent investigating travellers. Many of these travellers went to extraordinary lengths to test their accuracy, and always with affirmative results. Travellers and foreign residents verified them by personal experience and very frequently relied upon them for personal help. These assertions were met abroad by religious opposition because of the heathen relations of the coca customs, by very great professional conservatism, and, lastly, by discredit because the leaves, exported for use, largely failed, in the condition in which they were received, to verify them. All the present important uses of the drug in its own form, or in that of cocaine, cannot be said to cover the same ground involved by the native uses of coca leaves. There appears to be but one rational explanation of this broad discrepancy, namely, changes in properties which the leaves undergo after being dried. This view has been verified by the writer by numerous assays of the leaves soon after collection, compared with others made later. Preparations made upon the spot have also been found, by extended trial, to act more like the leaves as chewed by the natives than like preparations made from the exported leaves.

The details of the method of use have been so often published that any account of them appears scarcely necessary in this article. The use of *Llipta*, or ashes, with the bolus is to be regarded partly like that of condiments, especially of salt as such, without food. At the same time, the suggestion made by Holmes that the effect of this alkali is to decompose the alkaloid, cocaine, developing new constituents which exert the desired physiological action, is full of food for thought and experiment.

CULTIVATION AND PRODUCTION.—The product in use proceeds wholly from cultivated plants. Leaves from wild plants are unfit for use. Its cultivation is generally like that of the coffee and tea shrubs. Details will be found in the article last cited. Cultivation is very extensive in Bolivia, whence large quantities are exported to Peru for native use, in addition to the large quantities there produced. The annual consumption is to be stated in tens of millions of pounds. It is comparatively little grown outside of the two countries named, the product of Ecuador, Colombia, Venezuela, Brazil, India, Java, Mexico and other countries being chiefly of the other kinds. There is no point in the United States where the climate would admit of its being grown satisfactorily, though it would probably do well in the mountains near Santiago de Cuba.

The Coca Plant.—The shrub grows from five to eight feet high and is widely branched. The trunk may ultimately attain a thickness of four or five inches, and it, with the larger branches, soon becomes shaggy with gray lichens. The twigs soon become scaly with the closely set, stiff, almost spinose persistent stipules, and are densely leafy toward their ends. The small white or cream-colored flowers grow in little fascicles, close against the bark, on the older and leafless parts of the twigs. They are followed by an investment of ovoid, slightly inequilateral, smooth drupes, which become about a fourth of an inch long and of a deep-red color. The first crop of leaves can be gathered at about two and a half years from seed, and the shrubs bear well for twenty or thirty, or even forty, years. There are no definite months for picking, the condition of the leaves determining the time. Their development at the tip of the twig is continuous, and if allowed, they would as continuously fall off below, but they are picked just in time to avoid loss from this cause. The shrub yields two or three, or sometimes even four, crops in the twelve months. They are picked by hand and immediately dried in the sun