STUDIES IN EXPERIMENTAL CEREAL FOOD POISONING.

A Contribution to the Pathology and Etiology of Pellagra and Beri-beri

by

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I. INTRODUCTION

In all ages and in all countries where man has tilled the soil cereals have formed the main ingredient in the dietary of the people and an important part of the food of domesticated animals. Although from the earliest times of civilisation they have been valued as foods, their consumption as a staple diet may be followed by serious poisonous effects, and two notable diseases, pellagra and beri-beri, have long been popularly associated with maize and rice respectively. During the present century the conception has arisen of "dietary deficiency diseases" (the "Mangelkrankheiten" of German writers) which lays emphasis, not upon the positive presence of noxious material in the food consumed but upon the absence from the diet of certain essential constituents, commonly known as vitamins. The role of the vitamins is so widely accepted and so tacitly assumed, that the etiological relationship of their absence to pellagra and beri-beri is held by many authorities to be established. The investigations of Stockman (1917, 1929, 1931) into the poisonous principles of certain pulses directed attention to the question of the possible existence of toxic substances in cereals, and the present research, followed out in some detail in the case of maize and later embracing rice, wheat, rye, and oats, not only revealed the presence of poisons in these grains but re-opened the etiology and pathology of pellagra and beri-beri from a new angle.

II. GENERAL CONSIDERATIONS OF THE CEREALS INVESTIGATED

As grains these cereals are the edible farinaceous fruits (improperly but commonly termed "seeds") of cultivated grasses, wheat, oats and rye being the familiar cereals of temperate climates while maize and rice are extensively produced in the warmer parts of the globe.

Oats (*Avena Sativa*):

Unknown to the ancient Chinese and the peoples of India, oats were not cultivated by the historic civilisations of Egypt, Israel, Greece, or Rome. There is every reason to believe that this grain is a product, by selection and cultivation, of the wild oat (*Avena fatua*) a native of Europe, in which continent, as civilisation advanced, oats became an important grain-crop of the cool moist climates. The husked grain is used as meal, being richer in proteins and fats than wheat and possessing a high nutritive value. Oatmeal contains more calcium and phosphorus but slightly less carbohydrate than white flour yet Mellanby (1925) found in experimental work with puppies that this cereal produced the most severe rickets.

Rye (*Secale cereale*):

A hardy grain of cold climates, rye has been called

"the grain of poverty", a term descriptive both of the soil which rears it and the peasantry who live on it. Not so ancient as wheat, it is a native of N.E. Europe and in the middle of the nineteenth century was the principal sustenance of fully one-third of the population of Europe. Rye is usually eaten as bread and its association with ergotism is well known.

Wheat (Triticum sativum):

Wheat, the chief bread-food of the more highly civilised races, is a grain of great antiquity, its cultivation being older than the history of man. It was one of the most valued cereals of the ancient civilisations of Persia, Egypt, and Greece, but so far as is known was not grown in America before the days of Columbus. The only parts of the world where it is absent are the arid low-lying areas of the tropics. It is grown in every country in Europe and Asia (except Siam), in large areas of Australia and New Zealand, the Mediterranean Coasts, Abyssinia, Nigeria, and British East Africa. In the western hemisphere, besides the vast wheat fields of Canada and the United States, its cultivation has spread to Mexico and the republics of Central and South America.

Linnaeus (1753) mentioned five species (T. aestivum, T. hibernum, T. turgidum, T. speltum, and T. monococcum)

but through selection, hybridation, and mutation, there has been evolved an enormous number of varieties and forms from the original two or three wild species. At the present time, the countless varieties of cultivated wheat are classified into eleven natural groups. Owing to the peculiar physical and chemical properties of its gluten, wheat makes a more palatable bread than any other cereal.

Rice (Oryza sativa):

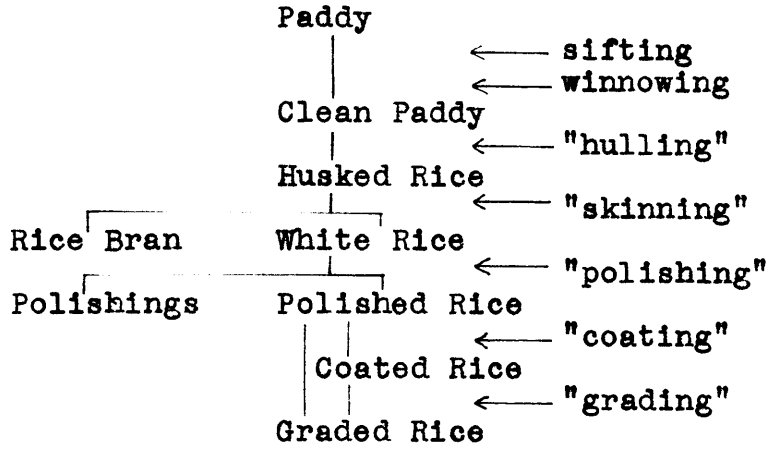
Rice is the great food of the Orient. The Sanskrit name ("Dhánga") means "the supporter (or nourisher) of mankind" and the commonly accepted origin of the name "rice" is the Tamil word "arisi" which denotes rice after removal of the husk. There are over 5,000 known varieties, each possessing such individual morphological features that the American Bureau of Agriculture classified as distinct varieties 990 out of 1280 samples tested. The rice of commerce is Oryza sativa, a grain possessing an outer golden husk, a cuticle varying from creamy white to mahogany red, a starchy kernel, and a germ which is readily removed in milling. Although chiefly grown in the East (including Egypt) less commonly known sources are Roumania, the Caucasus, Bulgaria, Greece, Italy, Spain, Carolina and Georgia in the United States.

In view of the relationship of rice to beri-beri and

the theories as to the cause and nature of that disease, the preparation of the grain is of considerable importance. Rice in the husk is known as "padi" or "paddy" from which, by various processes, several commercial varieties are produced. Modern machine milling, invented about the middle of the nineteenth century and applied to rice about 1885, comprises the processes of hulling, skinning, and polishing, removing in stages the husk, the cuticle, and the germ. Earlier methods of milling did not so thoroughly remove the cuticular and aleurone layers and the grain prepared by native races still retains more or less of the cuticle.

"Polishing" is effected by rotating the kernels of white rice against "flappers" (usually of felt), what is removed in the process being known as "polish". "Coating" is supposed to make the rice more shiny and attractive, talc and glucose being commonly employed, although steatite, mica, kaolin, and gypsum are also used.

In the course of the present investigations, great confusion has been found among grain dealers with regard to the nomenclature of the various types of marketed rice. The following table may be taken as representative of the important varieties with the steps in their production.



An important process which is largely used in the treatment of "paddy" is that of "parboiling" by which the grain is soaked for 24-36 hours, subjected for 15-20 minutes to steam at atmospheric pressure, and dried in the sun. This treatment facilitates husking but renders removal of the pericarp more difficult, and the grain is said to keep better.

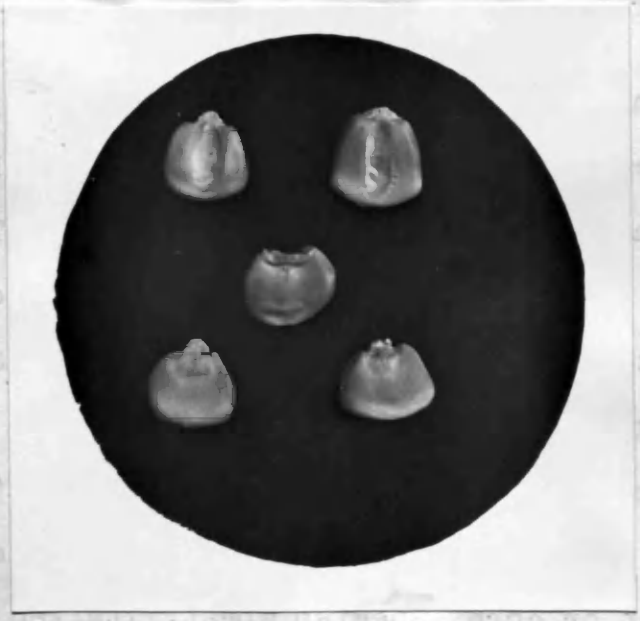
Among rice-eating peoples the ways of cooking the cereal are many and varied, but two common methods are worthy of note. By the one, in favour among Europeans in the East, the grain is so cooked that the kernels remain distinct and free, only as much water being used as will be absorbed by the rice or can be evaporated. On the other hand, the Orientals, who prefer a milder flavoured rice, use a large excess of water and drain off the surplus. In addition to its importance as the staple food of the East, rice is a source of alcoholic beverages, notably in Japan where the manufacture of "saké" is a nationally established industry,

scientifically operated and regulated, whereby rice is fermented by pure cultures of saccharolytic organisms. In India rice-beer is made by means of a ferment "bákhar". The excessive consumption of these alcoholic drinks not only produces intoxication but may induce chronic poisoning with tremors, palsies and other signs of nervous disorder.

Maize (Zea Mays):

Maize, one of the staple food-crops of the world, is almost certainly of American origin. Introduced into Southern Europe about 1500 A.D. by Spaniards and Portuguese, its distribution although widespread is limited by the climatic requirements for its cultivation, viz., heat, abundant sunshine and intermittent heavy rain. The indigenous grain of the American Continent, it is also extensively cultivated in Italy, Spain, the Balkans, Russia, South Africa, Lower Egypt, and has found place in India and China. The many synonyms applied to it indicate the country from which the grain was introduced into any given locality, e.g. Indian wheat or corn, Spanish wheat, Italian corn, Roman wheat, Sicilian wheat, Turkish corn, Barbary wheat, etc. The generic name Zea, applied by Linnaeus, is derived from the Greek "Zea", a feeding grain mentioned by Homer (Odyssey 4. 4. 604). The specific name "Mays", and the common word "maize" are derived from the original

Fig. 1. MAIZE GRAIN.



Spanish-American term "mahiz". Of the ten botanical varieties, six are regularly cultivated for the grain, and over 500 breeds are known.

Table of cultivated varieties of Zea Mays:

Variety	Common Name
Tunicata	Pod maize
Indentata	Dent maize
Indurata	Flint maize
Everta	Pop maize
Amylacea	Soft maize
Saccharata	Sweet maize

The grain is of familiar flattened-wedge shape varying in colour from reddish-yellow to white. In botanical terms, it is a fruit of the form known as a "caryopsis", in which the outer covering (pericarp) is completely united with the seed-coat (testa). The hull (husk, skin,) is the thin outer coat formed by the fusion of the pericarp with the testa, and lined on the inner side by a thin layer of tissue, the perisperm. It is removed in milling as "maize bran" and consists chiefly of carbohydrates (92%). Beneath the hull is the aleurone layer, also termed the "horny gluten", rich in protein and oil. It is yellow in colour and is not readily separated from the underlying starchy endosperm. In transverse section it appears as a thick, regular, single layer of deep, rectangular cells, and constitutes from 8%-14% of the entire grain. The starchy

endosperm, amounting to 70% of the grain, is composed of two parts, the outer translucent, corneous, "horny starch", and an inner opaque "white starch". The relationship between these two parts has been likened to that existing between ice and snow. The horny starch contains 10% protein and 89% carbohydrates, the white starch 8% protein and 91.5% carbohydrates. The apex of the grain, representing the site of attachment to the cob, consists of a small starchy cap, the tip cap, which forms a protective sheath for the embryo. The embryo lies partly embedded in the endosperm on that surface of the grain which faces the tip or distal end of the cob. It is rich in salts and contains approximately 80% of the oil of the whole grain. Mellanby (1931) has recently laid great stress upon the fact that yellow maize contains carotene, a substance lacking in the white varieties.

The percentage of ash in maize is small, consisting chiefly of phosphates of potassium and magnesium, with but traces of calcium and iron. The protein content averages 10%, the characteristic protein being zein which resembles somewhat the gliadin of wheat but is neither sticky nor plastic. There is a high proportion of starch with small quantities of sugar, dextrin, pentosans, and gum, and the grain is relatively rich in fat (chiefly existing as the

fixed oil), 80% of which is found in the germ. During the chemical investigations I obtained small quantities of an essential oil.

As a food maize is rich in starch and fat, poor in protein and salts, easily digestible, and "by far the cheapest food offered to mankind over a large part of the civilised world." (Henry 1901). The following table (Burtt-Davy 1914) places maize second only to wheat in the amount of available digestible nutrients:-

Total Digestible Nutrients in 100 lbs. of several Cereals:

	Protein	Carbo-hydrates	Fat	Total
Wheat	10.2	69.2	1.7	81.1 lb.
Maize	7.9	66.7	4.3	78.9 lb.
Rye	9.9	67.6	1.1	78.6 lb.
Rice	4.8	72.2	0.3	77.3 lb.
Oats	9.2	47.3	4.2	60.7 lb.

Maize is commonly used in the form of meal, made into bread or cakes, or cooked with water to form a pottage, methods of preparation which have varied but slightly since the days of the ancient Aztecs. In the United States a large industry has been established in the "canning" of cooked young grains, "canned corn" being a staple vegetable during the winter months. As with rice in the East, so maize in the West is the source of native alcoholic beverages, which are prepared by fermentation not only of the starchy

grain but also of the saccharine juice of the maize stalk. A rather unusual use of maize, now practically discontinued, was to be found in the days when coffee was neither plentiful nor cheap in South Africa, where the Boers used roasted maize grain as a coffee substitute.

III. FEEDING EXPERIMENTS

Numerous observations were made on the effects of feeding yellow maize meal, with an adequate supply of vitamins, to monkeys, rabbits and guineapigs. The meal was given as porridge, supplemented in the case of the monkeys, by butter, milk, and a liberal supply of fresh fruit. Rabbits and guineapigs received a supplement of fresh cabbage.

It early became apparent that some samples of maize were much more poisonous than others, a fact confirmed by the chemical analyses which clearly demonstrated that different supplies of the cereal varied greatly in their yield of active fractions. Similar results were found in a long series of experiments with other cereals by Professor Stockman.

The animals also showed individual variations in susceptibility to a maize diet, some of them proving much more resistant than others. In an attempt to increase the amount of active substance ingested by the monkeys, aqueous extracts of maize were used in cooking the porridge, but the animals refused to eat the food prepared in this fashion. The administration of watery extracts of maize by stomach tube was more successful, being followed invariably by depression and some paresis of the limbs.

Fig.2. MAIZE FEEDING.

Bonnet Monkey___ 35th day.

MONKEYS

Maize:

A. A Rhesus monkey, presumed to be in good health, was delivered to the laboratory about mid-day. In the early afternoon it received a feed of milk and porridge made from yellow maize meal and containing some butter. Next morning it was found dead. No naked-eye lesions were apparent and, unfortunately, the viscera were not retained for histological study. We concluded that this animal died from acute intoxication, an occurrence not unknown among pigs, sheep and cattle who have been turned into fields of lathyrus to feed (Stoekman 1917, 1929).

B. A Bonnet monkey (Macacus sinicus) was fed on a daily ration of 75 grms. yellow maize meal, 10 grms. butter, some wheat bran, 60 c.c. milk, and orange juice, with a supply of fresh fruit. It became progressively paretic and steadily lost weight. Fits of drowsiness alternated with periods of apparent mental alertness during which it ate its food with relish. General muscular weakness developed, affecting especially the extensors of the limbs and trunk, the animal crouching with bent knees, drooping head, and flexion of the elbows, wrists and fingers. On the 32nd day the fingers were so clenched that it could neither lift its food nor climb. With hips and knees

Fig.3. MAIZE FEEDING.

Bonnet Monkey---43rd.day.

in spastic flexion, it could only shuffle along, using the arms for support. By the 43rd day (Fig. 3.) the animal was stuporose and almost completely paralysed, death occurring the following morning (44th day). The weight at the beginning of the experiment was 1990 grms., falling to 1940 grms. (14th day), 1760 grms. (30th day) and 1505 grms. (43rd day).

Post mortem examination was begun within a few minutes of death. The flexor muscles of the limbs were firmly contracted, the fingers being tightly clenched on the palms. The subcutaneous and omental fat had almost disappeared and the skeletal muscles were pale and atrophic. The larger viscera appeared normal to the naked eye but the paracolic lymph glands were enlarged and of pinkish colour on section.

Histological Examination: The liver, spleen and kidney showed a minor degree of congestion of the smaller vessels. The abdominal lymph glands presented the picture of hyperaemia with loss of the typical architecture owing to an enormous proliferation of lymphocytes.

Sections of the brain and spinal cord stained by the Marchi method showed an early scattered myelin degeneration in the regions of the sensory nerve roots, the posterior and antero-lateral columns of the cord, and the

Fig.4. MAIZE FEEDING.

Rhesus Monkey ---36th day(immediately before death).

Note the wasting, flexion of limbs and digits.

internal capsule. In the mesencephalon, the sensory fillet and the fila of the oculomotor nerve were involved. Many examples of swelling, chromatolysis, and displacement of the nucleus, were found in the cells of the cervical posterior nerve roots and of the motor area of the spinal cord.

C. A Rhesus monkey was fed daily on 70 grm. yellow maize meal, 10 grm. butter, 60 c.c. milk, with a liberal supply of fresh fruit.

At the end of one week the right arm was paretic, with flexion of wrist and elbow, and adduction of the upper arm. This condition passed off but returned on the 22nd day. The following morning the maize porridge was cooked with a watery extract prepared from 200 grms. maize meal. The paresis increased, the animal steadily lost flesh, and the coat became thin and ragged. On the 34th day the animal sat hunched up, as if asleep, with flexion of the trunk and limbs, the head being supported on the bent knees. The lethargy deepened and the animal died on the 36th day. The organs were examined immediately.

Post mortem, the body was greatly emaciated with general loss of hair. All four limbs were contracted and the muscles wasted, but the viscera showed no visible changes. The cells of the hepatic lobules and the renal

epithelium showed some cloudy swelling. The bone marrow was healthy. Myelin degeneration was found in sections of the sciatic nerve, spinal cord and nerve roots, medulla oblongata, midbrain, corpus striatum and the cerebral cortex of the Rolandic area.

D. Several varieties of maize meal were fed to monkeys with the usual supplies of milk, butter and fruit. The only noticeable effect was slight weakness of the legs. Watery extracts prepared from 700 grms. and 1000 grm. of the meal, when given *per os*, produced a transitory drowsiness with some paresis of the hands and fingers.

Cereals other than maize.

Professor Stockman and his staff were engaged in the isolation of active substances from oats, wheat, rice and rye, and studied the effects of these cereals on several monkeys. I undertook the pathological examinations and employed the same methods as in the maize-fed monkeys.

E. A *Rhesus* monkey, fed on 100 grm. Scotch oatmeal, (as porridge), 10 grm. butter, 60 c.c. milk, and fresh fruit, had slight attacks of paresis of the arms and flexion of the joints. 0.25 grm. of the neutralised active principle of oats was given hypodermically on the 58th day, and 1 grm. of the sodium salt on the 92nd day.

Paresis set in within a few minutes of the first injection. The skin became intensely itchy and before long there was inco-ordination of the finer movements of the fingers. The animal leaned against the wall of the cage as if fighting against sleep, then at times lay down. During the next few days the paresis continued, the muscles were tremulous on exertion, the joints flexed, and movements were clumsy. The animal never returned to normal. After the second dose (92nd day), it rapidly became very helpless and drowsy, with twitching of the muscles, followed later by flexion of all limbs. Just before death it was semi-paralysed and was killed by chloroform on the 96th day.

Compared with the maize-fed monkeys the wasting was less severe, and the muscles were well preserved. Some enlarged lymph glands from the ileocaecal angle were found to have focal congestion of the intraglandular capillaries with associated proliferation of lymphocytes. Many multipolar cells in the lumbar region of the spinal cord were swollen and showed chromatolysis. In the superior cervical ganglion, strands of young fibroblastic tissue separated masses of nerve fibres and poorly-staining ganglion-cells. Many cells in the stellate ganglion were swollen, with blurred nuclei, and devoid of Nissl granules except for crescent-shaped accumulations around the periphery

of the cell. The sciatic nerve, the sensory columns of the cord, and the medulla oblongata were degenerated.

F. A Rhesus monkey, receiving a daily ration of 100 grm. oatmeal for 66 days, developed a mild paresis of the limbs. The cereal was replaced by a liberal mixed diet and in 3 weeks the animal made a good recovery except for some slight wrist-drop. 1.4 grm. of the neutralised active acid (somewhat impure) was then injected into the left flank. It soon became very paretic and was much worse on the following day, but owing to irritation around the site of the injection it was killed by chloroform. No special changes were found in the viscera but the nervous system showed the usual degeneration in the peripheral nerves and spinal cord.

G. A Rhesus monkey, fed on rye, developed paresis, muscle twitchings and tremors, and was killed on the 102nd day of the experiment. It was very thin and emaciated. There was congestion of the liver, spleen, and kidney with numerous deposits of blood pigment, the liver cells were granular, and the renal epithelium showed cloudy swelling. Typical early myelin change was found in the nervous system but, in this instance, the pyramidal tracts were definitely affected.

H. A small Rhesus monkey was given per os an aqueous extract prepared from 2000 grm. Rangoon rice. Except for

slight weakness which persisted, it remained quite active. A fortnight later a watery extract of 200 grm. highly milled Carolina rice was given once daily for 5 days. General muscular weakness developed, affecting the arms, legs and loins. At further intervals extracts from 400, 800, 1000, and 2000 grms. of the same rice were administered but, although the feebleness and debility became progressively worse, the effects were not in proportion to the increased dosage. 30 days after the first Carolina rice-extract was given, the animal was killed. The viscera were all healthy, no myelin changes in the nervous system were found, but many nerve cells in the spinal cord and posterior root ganglia were swollen and devoid of chromophile granules.

I. A Rhesus monkey, fed for 10 days on a diet containing 120 grm. Scotch wheat, was given by stomach tube a watery extract from 400 grm. ground wheat. The animal became very drowsy and ultimately comatose, dying 6 hours after the administration of the extract. Post mortem examination was begun at once.

Post mortem notes.

A well-nourished animal. No contractures.

Stomach: Flaccid. Contains 2 fluid ounces of green viscid fluid. Hyperaemia of lesser curvature.

Liver, spleen, kidney: All intensely congested. On section, blood oozes freely from cut surfaces.

Heart and Lungs: Normal.

Brain: Engorged pial vessels. On transverse section the thalamus and corpus striatum show punctate oozing.

Spinal cord: Minute sub-pial haemorrhages. On section the grey matter stands out as a salmon pink area.

Histological Examination:

The vascular network of the liver was intensely congested and the lobules showed widespread cell damage, varying from cloudy swelling to complete necrosis. The spleen was distended with blood and the kidney presented the picture of an acute toxic nephritis. No myelin change in the nervous system could be detected in numerous serial sections, but the damage to the cellular elements extended from the cortex to the peripheral ganglia. The spinal vessels throughout the whole length of the cord were engorged, and in the lumbar region minute extravasations of blood displaced whole groups of cells in the ventral horns. Many multipolar nerve cells were compressed and distorted, lying bathed in fluid, others were swollen, opaque, and devoid of all chromophile granules. In the brain, especially in the optic thalamus, the appearances were those of pericellular oedema with vascular engorgement and poorly staining cells.

The pathological picture in this case was what I have termed a "pathological explosion". The monkey died of acute poisoning following a massive dose, which, by its irritant effects, seriously damaged the liver and kidney, and wrought widespread havoc on the specialised cells of the whole nervous system.

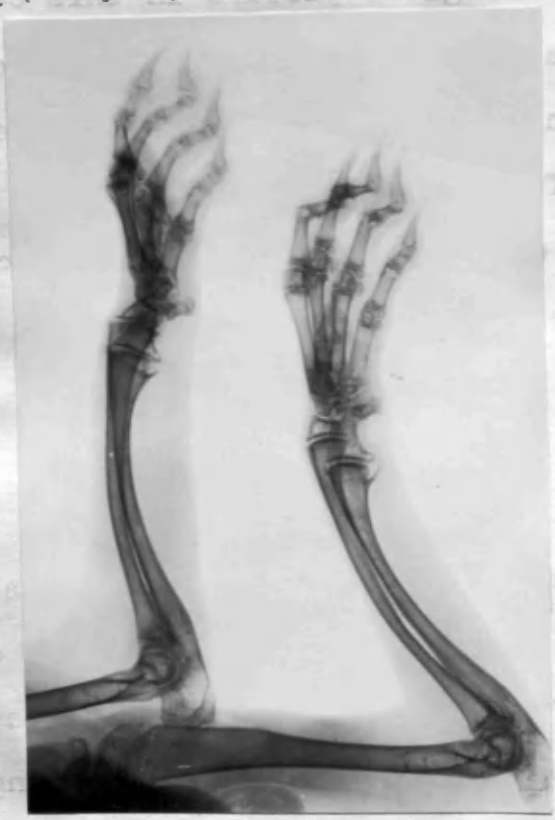
R A B B I T S

Several series of rabbits were fed on a liberal supply of yellow maize meal, with 70 grms. fresh cabbage daily. Their progress was observed from day to day and compared with that of control animals. With one exception, none of the rabbits fed on maize throve, young rabbits faring badly as compared with more mature animals. Whenever maize meal was replaced by wheat bran, an immediate improvement took place. In the initial stages of maize feeding there was generally some gain in weight, but the rate of growth slowed down, or the animal began to lose weight steadily. Loss of hair and dry scaling of the skin occurred in the majority of cases, but the general results varied greatly even among members of the same litter, some animals gaining in weight and retaining their fur, others rapidly becoming emaciated and bare. Sections of affected skin, when compared with those obtained from a healthy animal, showed keratosis, atrophy of the hair follicles and

RADIOGRAMS illustrating DECALCIFICATIONof BONE.

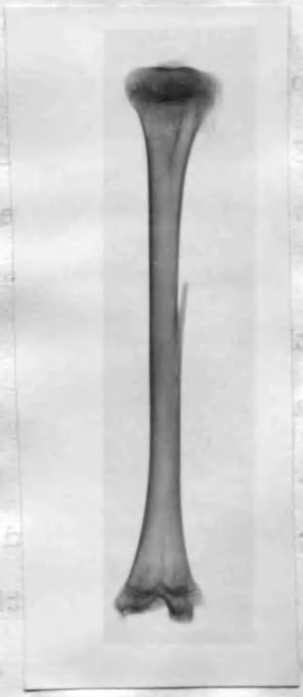
Rabbits fed on Maize (see p.22).

I. Forelimbs.



II. Femur

III. Tibia.



glands, with fibrous changes in the corium. All fatal cases lost weight, one dying in clonic convulsions (89th day), another becoming ataxic and paretic (101st day), while the others died from exhaustion.

As the wasting progressed, the legs were apt to become bent, in severe cases the forelegs being splayed outwards. Radiograms showed general decalcification of the bones and post mortem the affected bones were merely delicate shells. X-ray and histological examination proved the epiphyses to be normal, thus differentiating the condition from rickets. The effects would appear to be due to an acidosis, with consequent depletion of the calcium reserves to maintain the acid-base equilibrium of the body. Weiske (1894) found depletion of bone calcium in rabbits fed on oats, and with the same cereal an acidosis has been induced in rats (Morgen & Beger 1915) and in rabbits (Funk 1916), which could be prevented by adequate doses of sodium bicarbonate.

Examination of the nervous system yielded few positive results. In one rabbit, which became profoundly paretic before death, the posterior and lateral columns of the spinal cord were slightly degenerated. In no instance were the nerve cells of the brain affected but several cases showed definite chromatolysis in the root ganglia and

spinal cord. At first I thought that the chromatolytic change might be due to histological artefact, but so many control sections from healthy and diseased animals were studied, prepared simultaneously with, or under the same conditions of fixation and staining as the sections in question, that the authenticity of the histological appearances was established beyond doubt.

GUINEAPIGS

Guineapigs, fed on maize with a liberal supply of fresh cabbage throve and gained in weight. In four guineapigs, where the cabbage was replaced by orange juice, signs of malnutrition soon appeared, but recovery rapidly followed when green cabbage was restored to the diet. In another experiment, where cabbage was omitted, the addition of 1 c.c. cod-liver oil to the diet did not prevent the deterioration in weight and condition. Again the addition of cabbage ad libitum was curative and the animals ate less maize. These experiments proved that the malnutrition was not due to the absence of the cod-liver oil vitamins or of vitamin C. It would appear that maize itself was responsible, cabbage not only providing a supply of alkali but indirectly reducing the consumption of cereal.

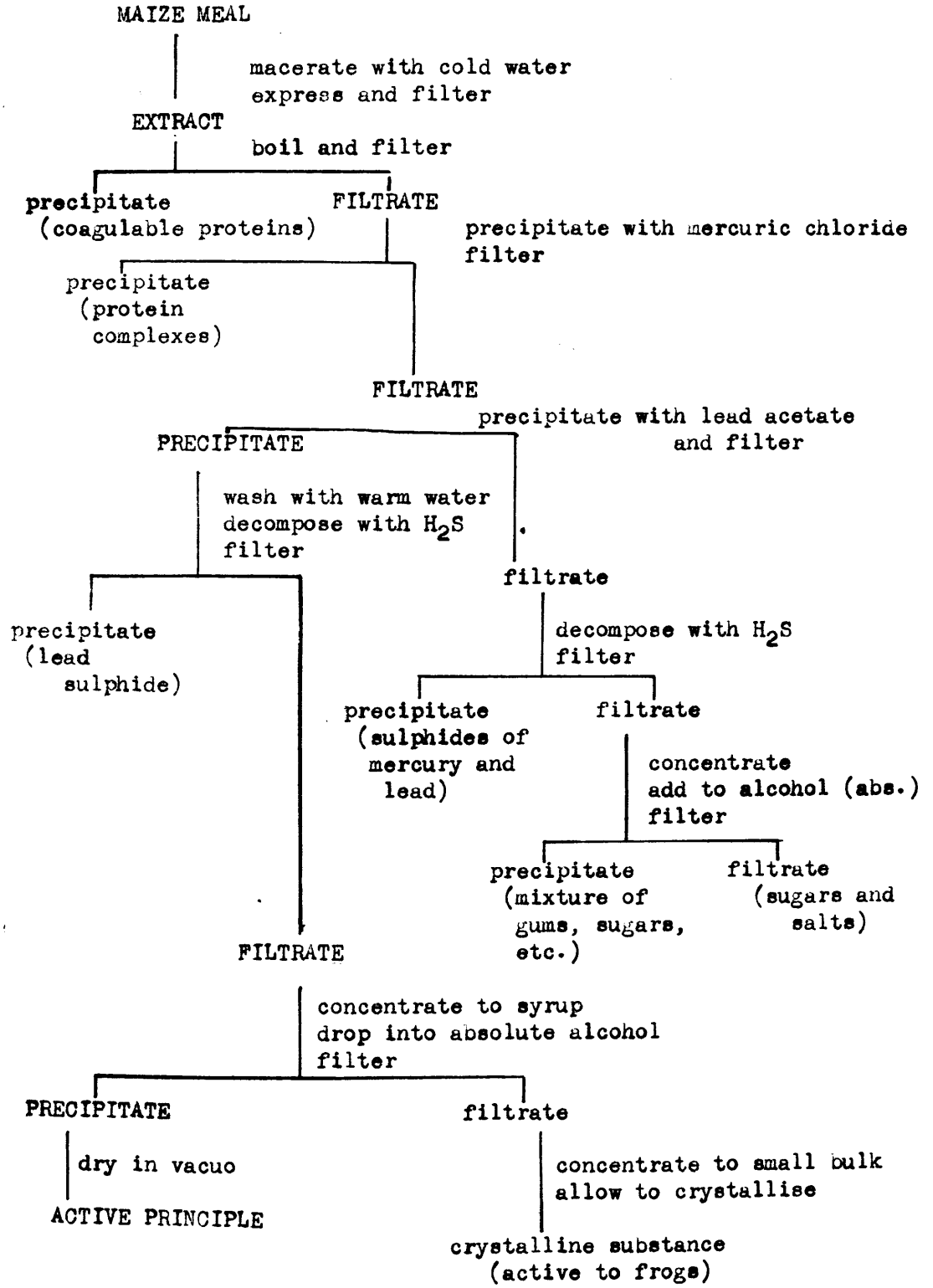
The feeding experiments indicate that, even with an adequate supply of vitamins, the cereals investigated can produce toxic symptoms. Different lots of the same cereal vary in toxicity, their potency probably depending upon their source and the conditions of their cultivation. The poisonous principles of different cereals may not be chemically identical but pharmacologically they are very similar in their effects. Watery extracts of poisonous varieties contain the toxic factor which is of an irritant nature, capable of damaging the liver and kidney if absorbed in massive dose or in smaller quantities over a long period of time. These poisons have a peculiar affinity for the essential cells of the nervous system, especially those of the sympathetic and nerve-root ganglia and of the large multipolar cells of the spinal cord. Further discussion of their action will be resumed in the chapter on their pathological effects.

IV. THE ISOLATION AND THE ACTION OF THE ACTIVE SUBSTANCE FROM MAIZE

Following the technique adopted by Stockman (1931) in the examination of certain leguminous seeds, 1-2 kilogramme lots of commercial yellow maize meal were used in the preliminary investigations. Acidulated water, chloroform water, and 25% alcohol were found to be the most useful extractives, yielding clear extracts from which coagulable protein could be removed by boiling. Using mercuric chloride, lead acetate and basic lead acetate as precipitants (vide Table p.26) twenty-four fractions were separated. Mercuric chloride completely removed the non-coagulable protein, while the basic lead acetate fractions yielded sugars, starches and oils. Tests on frogs indicated that the products derived from precipitation by lead acetate, although chemically impure, were alone active.

In later work, directed to the removal of contaminating sugars and oil, attention was directed to maize feeding-cake and maize germ, supplies of which were obtained from a well-known corn-flour factory. The process of manufacture entails the soaking and washing of 100 ton lots of maize in large vats, the washings being termed "steep water", a clear acid fluid from which, by concentration and dessication, "steep solids" are obtained as a brownish powder

TABLE showing PLAN of CHEMICAL ANALYSIS.



with no toxic action on frogs. The softened, swollen maize is crushed, and the endospermic starch removed by churning up with water. The residue of the grain, washed and dried, is transferred to a powerful hydraulic press which removes the fixed oil and delivers maize feeding-cake in large slabs, containing only a minimum of starch and fixed oil. These cakes were ultimately chosen as the source of the active principle and a technique was evolved which gave a final yield of 2-3 grammes of active substance per kilo. Samples of maize germ were tested but, although a very active product was obtained, the high proportion of oil in the germ presented an insuperable obstacle to purification of the end-product.

Method of Isolation of Toxic Substance from Maize Feeding-Cake:

Five kilogrammes of crushed cake were macerated for some days with water to which a trace of chloroform had been added as an antifermentative. The marc was expressed and the filtered extract boiled to remove coagulable protein. The large volume of filtrate was concentrated by distillation in vacuo at 20° C., transferred to a large cylindrical vessel and lead acetate added to slight excess. The copious white precipitate was washed with hot water until the washings were neutral to litmus and free from lead and carbohydrate. The washed precipitate was decomposed by H_2S, the lead-free

filtrate concentrated *in vacuo* to the consistence of a thin syrup and slowly dropped into a large excess of absolute alcohol. The white flocculent precipitate so obtained was washed with fresh alcohol and dried in a dessicator.

The final product is a fine amorphous white powder, freely soluble in water, dilute alcohol, insoluble in absolute alcohol, ether, chloroform and acetone. It contains no protein, amino-acid, glucoside or saponin, and gives no precipitate with the usual alkaloidal reagents. The aqueous solution is clear, faintly straw-coloured and very acid. Careful neutralisation with sodium bicarbonate produces a precipitate consisting of inorganic and organic impurities, and the filtrate, concentrated *in vacuo* and slowly dropped into absolute alcohol, yields the sodium salt of the acid. The salt is a stable, white, tasteless powder, readily soluble in water to form a clear neutral solution. This substance is an active poison which, although neutral to litmus, proved extremely irritant when injected subcutaneously into monkeys, rabbits, and guineapigs.

The Action of the Sodium Salt of the Active Acid:

Frogs: Doses of 0.02 gm. given hypodermically produced early exaggeration of reflexes followed by depression and paralysis which wore off in 24 hours, leaving a condition of increased excitability lasting for 2-3 days. Larger doses

(up to 0.05 gm.) produced rapid paralysis followed by death. Immediately after death the paralytic muscles and peripheral nerves reacted to the faradic current.

Kymographic experiments showed that a 1% aqueous solution had no action upon the heart, skeletal muscle or peripheral nerve.

Example I.

16.10.31.	9.50 a.m.	0.02 gm. into dorsal sac of small frog.
	9.55 a.m.	Very slightly affected. Reflexes increased.
	10.15 a.m.	Depressed. Inco-ordination. Reflexes markedly diminished.
	10.30 a.m.	More depressed. Reflexes abolished. Weak inco-ordinate movements on pinching.
	11.30 a.m.	Motionless. Rapid fibrillary twitchings of leg and toe muscles. Remained paralytic all day.
17.10.31	9.30 a.m.	Depressed but reflexes exaggerated.
18.10.31		Moves freely. Reflexes brisk.
19.10.31		Normal.
20.10.31		Normal.

Example II.

16.10.31.	10.17 a.m.	0.05 gm. to large frog.
	10.45 a.m.	Marked paralysis. Abortive attempts to move on pinching.
	11.45 a.m.	Complete paralysis.
	2.30 p.m.	Dead.

Rabbits:

Hypodermic injection of 0.5 gm. into the subcutaneous tissue of the flank had no effect upon the nervous system, but produced violent local irritation followed by tissue necrosis. Microscopical examination of the phlegmonous area showed mild hyperaemia and leucocytic infiltration, with coagulative necrosis of muscle fibres subjacent to the site of injection. Careful intravenous administration of 0.2 gm. either killed immediately or had no effect.

Intravenous injection of sodium salt in rabbits:

Examples:

A.	8.4.31. Weight 925 grm.	Maize meal with 40 grm. cabbage.
	16.9.31. Weight 800 grm.	In miserable condition - has lost much fur, forelegs weak and bent, Put on diet of wheat bran and cabbage.
	26.11.31. Weight 1478 grm.	In good condition. Hair has grown well, forelegs still bent and slightly weak.
	2.12.31. Weight 1505 grm.	0.3 grm. sodium salt (maize) intravenously. Became paralytic almost immediately and died 10 minutes later.
	Post mortem:	Heart in fibrillation for 5 minutes after section. No histological changes found.

B. 8.4.31. Weight 840 grm. Maize diet commenced.

26.11.31. Weight 1550 grm. General condition good but marked loss of hair.

2.12.31. 0.25 grm. sodium salt (maize) in 1 c.c. distilled water intravenously. Immediate death due to cardiac asphyxia, suggestive of anaphylaxis. No histological changes.

C. Rabbit on normal diet.

9.11.31. 0.25 grm. sodium salt intravenously (slowly given). No change.

10.11.31. 0.32 grm. slowly given intravenously. Asphyxial convulsions with rapid recovery.

D. Rabbit on normal diet.

2.12.31. 0.6 grm. sodium salt intravenously. No effect.

The control rabbits stood large doses of the sodium salt when given intravenously, but those already affected by maize feeding died rapidly from a condition not unlike anaphylaxis.

One of several animals surviving injection was killed and examined but no histological changes were found in the liver, spleen, kidney or central nervous system. It is evident that the rabbit can rapidly detoxicate the injected poison, a fact which substantiates the conclusion arrived at from the feeding experiments that some rabbits may be

Effect of hypodermic injection of sodium salt of maize active acid.

Rhesus monkey (vide p.32).

Fig. 5.

2.10.31.

Fig. 6.

9.10.31.

Fig. 7.

10.10.31.

comparatively insusceptible to certain cereals.

Monkeys:

A. A Rhesus monkey was fed on a liberal diet of fruit, bread, butter and milk.

2.10.31. 1 grm. of the sodium salt was given hypodermically into the left flank. Within one hour there was intense itching of the skin over the lower limbs and back, followed by gradually increasing drowsiness and discinclination for food. The following morning the animal was still depressed, with some paresis of hands, arms, and hind limbs, noticed first of all by the animal dropping like a stone when attempting to descend from the roof of its cage. These slight but definite signs persisted for three days and thereafter passed off.

9.10.31. 1 grm. was injected subcutaneously into the right flank. Itching of skin and restlessness began shortly after the injection, but the depression set in much more rapidly and more markedly than on the first occasion. Within two hours the animal sat crouched upon its haunches, head sunk on breast, and, when roused, showed inco-ordination of movements. Next day, 26 hours after the injection, all limbs were paretic, with marked flexion of fingers and toes, generalised weakness, and somnolence. It was thereupon killed under chloroform (10.10.31).

Although the salt was given in neutral solution, it produced profound irritation of the subcutaneous tissues. Within 48 hours of the first injection there appeared a large circular patch of bluish discoloration which gravitated ventralwards to the hypogastric region, presenting on the fifth day a clean-cut ulcer, with reddish base and serosanguinous discharge. There did not appear to be any pain, although there was itching around the edges. Post mortem examination showed widespread adhesions of the parietial peritoneum below the sites of injection, the whole of the descending colon and a large part of the great omentum being firmly adherent to the abdominal wall. The site of the second injection (given 26 hours before death) showed serous exudation in the related area of the subcutaneous fat.

The liver showed some granular change, the spleen was somewhat hyperaemic, and the renal vessels were congested, with cloudy swelling and desquamation of the tubular epithelium.

The anterior polar cells of the spinal cord were swollen with loss of the characteristic stellate shape, and there was evidence in some instances of early granular degeneration. The superior cervical ganglia showed definite perinuclear chromatolysis. While the cord had

Sodium salt of maize acid per os, (vide p.34).

Fig.8. 24hours after second dose of Igrm.

6.11.31.

Fig.9. 2 hours after third dose of I grm.

6.11.31.

only a slight diffuse myelin change, the restiform body and the roots of the hypoglossal and accessory nerves showed clear evidences of degeneration.

B. The neutralised salt was given by means of stomach tube to a Rhesus monkey receiving normal full diet of fruit, milk, etc.

1 grm. was administered on the 4th, 5th, 6th and 7th November, 1931, (a total of 4 grms. over four days).

2 grm. were administered on the 18th, 20th, 23rd November, 1931. Death occurred on 24th November, 1931, in profound coma.

During the first period, 1 grm. doses of the active white powder were dissolved in 30 c.c. of water and given by stomach tube on four consecutive days before breakfast. Within two hours of the first dose the animal became restless, and appeared to be suffering from itching of the skin of the arms, legs and back. Between the 4th and 6th hours there was listlessness and drowsiness, with drooping of the head and loss of precision in the finer movements of the fingers. Next morning it had apparently recovered. The same cycle of events recurred after each successive dose with more definite drowsiness and finally some residual paresis. Owing to lack of material after the fourth dose had been given, an interval elapsed of eleven days before

Sodium salt of maize acid per os, (vide p.35).

Fig. 10. After second dose of 2 grm.

Fig. 11. Condition immediately before death.

(Coma, paralysis, contractures).

a fresh supply was ready. The paresis passed off and the monkey became quite active. Three doses of 2 grm. were then given with more pronounced effects. 24 hours after the first dose the animal was markedly depressed although still inclined for food. On the following morning there was definite paresis of both hind limbs and of the hands. On walking, it swung the hind limbs stiffly forward, using the fore limbs as crutches, pivoting on the extensor aspect of the clenched hands. The second dose of this series intensified the clinical picture. 48 hours after this portion was given, the fingers and wrist joints were in such acute spastic flexion that the animal could neither grasp nor lift food. It sat crouched on its haunches scarcely able to shuffle along. The neck and masticatory muscles were unaffected. When left in quiet it periodically drowsed, awaking with a start as the head fell sharply on to the chest. The final dose of 2 grm. was given on the 23rd November, 1931, and at 7.30 a.m. the next morning the animal could not be roused. Two hours later the breathing became stertorous, the coma deepened rapidly and death occurred 26 hours after administration of the last dose, with the animal lying coiled up owing to the generalised flexion of the trunk and limbs.

Post Mortem Examination:

Spastic contracture of fingers, wrists, elbows and toes. Nothing apparent in viscera to the naked eye.

Liver: Iron and pigmentary changes were absent. The intralobular capillaries were congested, the Kupffer cells large and deeply stained. The protoplasm of the liver cells was granular and vacuolated, their nuclei poorly stained. In some areas there was complete loss of typical liver structure, the orderly columns being replaced with irregular masses of necrotic cells.

Spleen: The splenic pulp was engorged. In the Malpighian areas, the lymphoid element was distinguishable only as a peripheral ring merging into a disordered arrangement of strands of cells enclosing large irregular spaces.

Kidney: There was congestion of the interstitial vessels. The convoluted tubules were slightly granular with pale nuclei. In scattered areas the free edges of the cells were ragged and the lumen blocked with granular debris.

Stomach and Bowel: Normal.

Nervous System: On section, the spinal cord and corpus striatum showed pinkish coloration of the grey matter. Microscopically, this was seen to be due to distension of minute capillaries with occasional extravasations especially

in the lumbar region immediately ventral to the central canal. The nerve cells showed areas of pericellular oedema, and typical chromatolysis. The posterior root ganglia and sympathetic ganglia were also involved in the characteristic Nissl degeneration.

V. The PATHOLOGY of the CHANGES in the NERVOUS SYSTEM.

Histological Methods:-

Having specially in view the histological examination of early changes in the central nervous system, all due precautions were taken from the outset lest the findings should be vitiated by errors of technique. As the research proceeded, and particularly when the illustrations provided in the literature were critically examined, the necessity for such precautions became more obvious, and for some months experiments were carried out to test the effects of various fixing and staining methods. It is essential that tissues from the nervous system should be adequately fixed as soon as possible after death, to eliminate post-mortem change and to avoid the effects of faulty fixation. A large number of preparations used in the literature to illustrate chromatolysis of nerve cells are valueless, as they show clear evidence of poor fixation or faulty staining, with resultant histological artefacts which can be reproduced experimentally.

With one exception, all animals examined were dissected within a few minutes after death, and the viscera rapidly removed and fixed. In the case of the monkeys, especial care was taken to remove the brain and spinal cord without

damage by pressure or traction, and by careful dissection it was found possible to expose and remove the posterior root ganglia attached intact to the cord. Removal of the sympathetic ganglia presented difficulty until preliminary anatomical study enabled me to devise a neat and rapid method of exposing and removing the superior cervical, stellate, and abdominal ganglia.

Method for staining nerve-cells:

Using equal parts of saturated solutions of picric acid and corrosive sublimate as a fixative, thin slices of tissue were fixed immediately, and after dehydration with cautious gradations of alcohol, ~~and~~ three successive paraffin baths were used before imbedding. Great care is necessary for these steps as the essential cells of the brain, spinal cord, and ganglia require the most delicate treatment. Sections of 5 μ were stained with a 1% aqueous solution of thionin or toluidin blue, and decolorised with absolute alcohol or acetone.

Method for demonstrating nerve-fibre degeneration:

In the present series the changes were so recent that the Weigert-Pal technique was found impracticable, and Orr's modification of Marchi's method was finally adopted for routine work. After fixation for 2-4 weeks in Müller's

fluid, thin slices of tissue were stained in a solution of 4 parts 2% osmic acid, with 1 part 1% acetic acid. Busch recommends formalin fixation and a stain of 1 part 2% osmic acid, 3 parts sodium iodate, and 300 parts of water. By this method the background remains almost colourless but unless the formalin has been removed by thorough washing, irregular black granules are sometimes found scattered throughout the section, apparently due to either some impurity in the formalin or too long fixation. Busch's stain was ultimately used to corroborate the ordinary Marchi reaction.

A number of experiments were undertaken with a view to the study and elimination of artefacts. It was found that early fixation, the use of thin slices of tissue, and the most gentle manipulation during the imbedding process were essential to secure clear sections. Formalin fixation is apt to produce a picture suggestive of myelin degeneration, but if a period not exceeding 24 hours in formalin is allowed for, with subsequent thorough washing in water, the tissues may be transferred to Müller's fluid and thence to the Marchi stain. Fresh supplies of osmic acid should be added to the staining solution every second or third day, and after removal from the stain, the tissues should be washed for several hours. Rapid dehydration and imbedding are essential as the stain is liable to be extracted in the process.

It should be noted that with overfixation of tissue, black granules (the "pseudo-granulations" of Marchi) are found scattered promiscuously throughout the section but are "interfibrillar", i.e. external to the myelin sheath.

The Pathological Histology of the Nervous system:

The pathological changes in the nervous system of monkeys induced by feeding with maize and other cereals, or by their toxic constituents, were investigated in some detail. In monkeys whose diet is largely composed of certain cereals or to whom the active products of these cereals have been administered, there appears progressive mental dullness, difficulty of locomotion, increasing weakness for co-ordinated movements, tremors of the limbs and rigidity, followed by stupor and death. Pathologically there is a diffuse myelin degeneration of the nerve elements of the cerebrospinal and autonomic systems associated with chromatolysis of the nerve cells. The changes produced by the active products are more acute than those in the feeding experiments, but clinically and pathologically the syndrome presented is that of a subacute combined degeneration of toxic origin.

The Nature of the Nerve Fibre Degeneration:

The site of attack in the nerve-fibres is the myelin or medullated sheath. The initial changes, which probably

Fig. I2. Cauda equina. Marchi stain. High power.
"Signet-ring" stage.

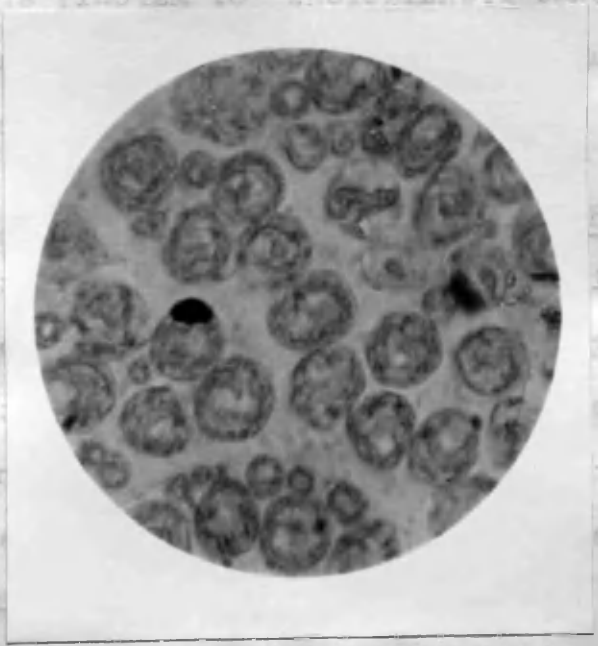
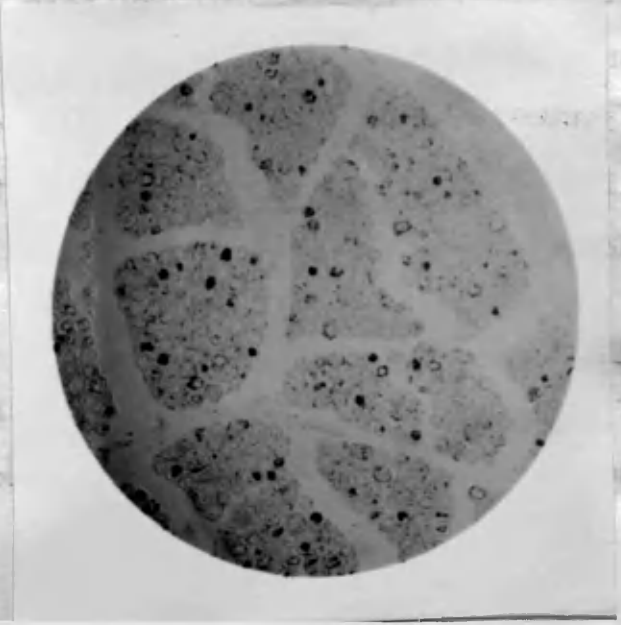


Fig. I3. Cauda equina. Marchi stain. Low power.



give rise only to functional disorder, are not demonstrable by present methods of investigation, but as the process advances the myelin disintegrates into fine droplets of unsaturated lipoid material which stains black with osmic acid. The earliest stage noted is illustrated in Figure 12, where in transverse section the stained degenerated myelin produces a "signet-ring" appearance. As the change advances the axon is encircled by a ring of Marchi-staining material and in longitudinal section the degeneration may be traced as a chain of black globules. Mellanby invariably uses the term "demyelination" in connection with such changes but this nomenclature is misleading as the myelin although degenerated is not removed. The condition is a parenchymatous degenerative lesion of the nerve-fibres both in the cerebrospinal axis and in the peripheral nerves, but the traditional nomenclature of parenchymatous peripheral neuritis, based upon the coarse anatomical conception of a "nerve" is inadequate for descriptive purposes.

The Anatomical Distribution of Nerve-Fibre Degeneration:

Although it can be traced from the peripheral nerves up to the cerebral cortex, the degeneration is not confined to any anatomical division of the spinal cord or brainstem, but is diffusely scattered and surprisingly symmetrical in distribution. The number of affected fibres varies greatly.

Fig. I4. Cervical root ganglion. Marchi. Low power.

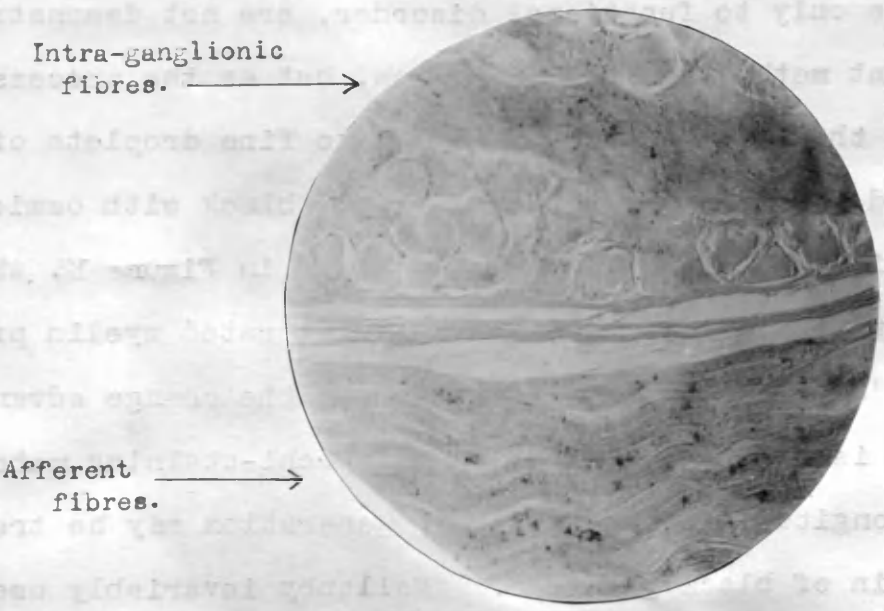
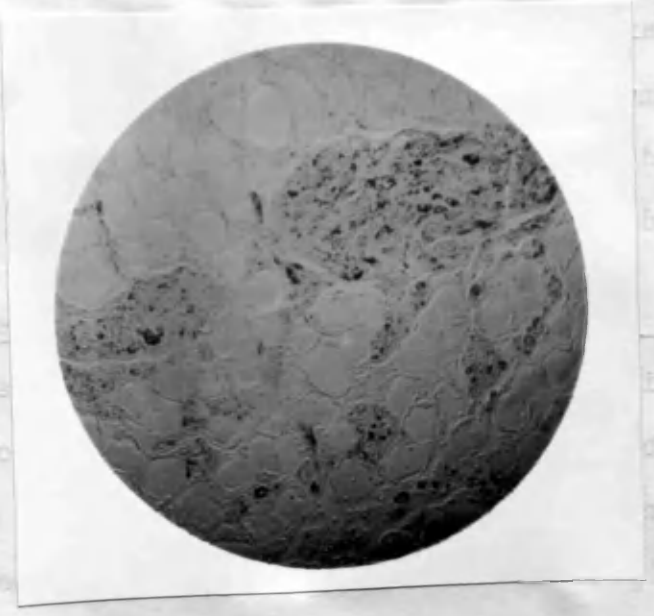


Fig. I5. Lumbar root ganglion. Marchi. Low power

Intraganglionic fibres degenerated.



When few, they appear isolated amid small patches of healthy tissue, while in other instances normal myelinated fibres are relatively few. The cauda equina, and the cervical and the lumbar enlargements of the cord show the earliest and most marked change, especially in the regions of the posterior nerve roots and columns. The degeneration may be traced from the peripheral somatic nerve trunks via the nerve-roots into the grey matter of the spinal cord. On the sensory side the afferent and efferent fibres of the posterior-root ganglia are affected in proportion to the degree of involvement of the posterior columns of the cord, especially at the point of entry of the roots at the tip of the posterior cornua. Strands of medullated fibres passing from the region of the posterior columns into the grey matter of the posterior horns, the motor nerve roots, and the fila issuing from the anterior cornua are similarly involved, but the ground bundles adjacent to the grey matter show no visible change. In the lateral area, the spino-cerebellar (Flechsig & Gower), the spino-thalamic, and the spinotectal tracts are generally damaged but the pyramidal and other descending bundles are not so deeply involved.

In the medulla oblongata, degeneration occurred in the regions of the restiform body, the mesial fillet and the peripheral areas, while in one case the fila of the accessory and hypoglossal nerves stained deeply with osmic

Fig. I6. Midbrain. Marchi. Low power. (vide p.44).

Oculomotor nerve fila.

acid. The cerebellum was affected to a variable extent, the usual site being around the dentate nucleus. In the midbrain there was a slight involvement of the crus and antero-lateral region but the mesial area of the fillet was especially marked. In one monkey fed on maize the oculomotor fila stained deeply (Figure/6). The degenerated fibres in the cerebrum were fairly numerous, running in definite strands in the internal capsule especially at the level of the thalamus.

Of the peripheral nerves the sciatic, internal popliteal, and musculospiral nerves were examined and showed the typical parenchymatous degeneration.

The Nature and Distribution of the Nerve-Cell Changes:

When stained with thionin or toluidin blue, the histological appearances of the normal posterior-root ganglion cells in the monkey vary according to the types of cell present in a given section. At least three varieties occur, having in common a well-defined achromatic nucleus with deeply staining nucleolus, but they differ in the size, distribution, shape, and staining propensities of the chromophile (Nissl) granules. There is a well-defined unstained perinuclear space, outside of which the chromophile elements may be distributed irregularly, concentrically, or in a vorticose arrangement, in each type the granules

Fig. I7. Normal root ganglion. Thionin. Low power.

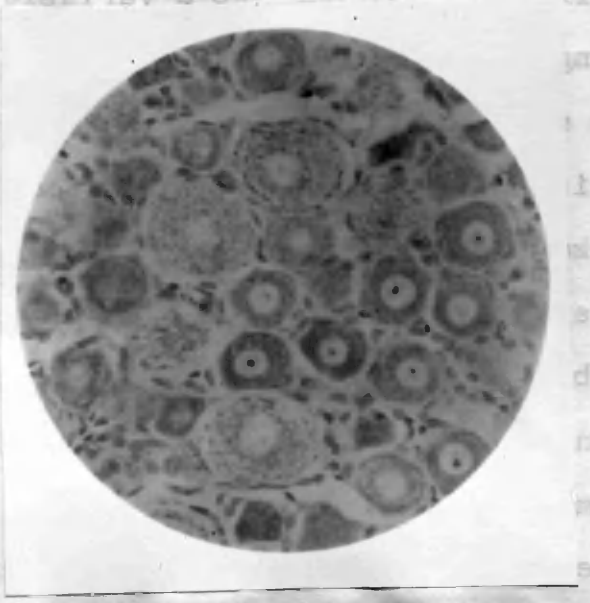
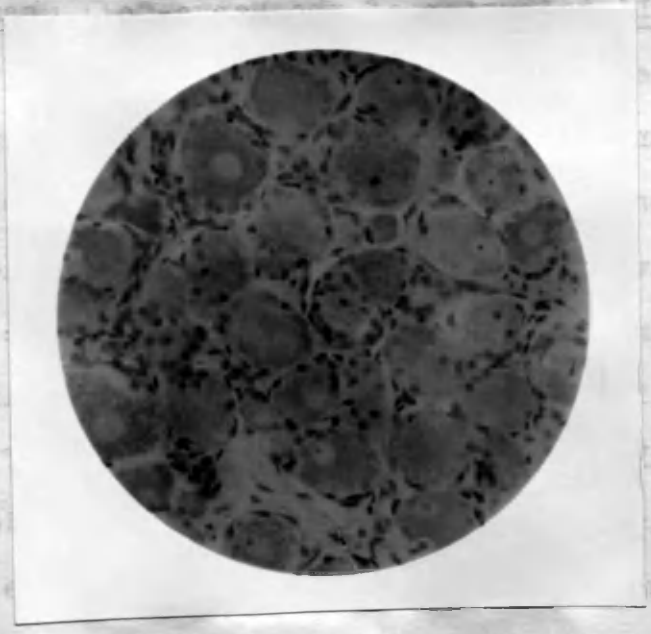


Fig. I8. Root ganglion. Thionin. Low power. Chromatolysis.



being sharply defined and uniformly stained. In type I, the cells are large or medium-sized, the Nissl's granules small, discreet, and lightly stained, except for a peripheral ring composed of a single layer of large deeply staining granules. Type II consists of large or medium cells packed with deeply-staining chromophile elements. In type III the nucleus is slightly eccentric and is surrounded by angular well-staining granules which are connected by fine chromatic filaments arranged in whorls around the nucleus (the "vorticose cell" of Lugaro). Here and there are small deeply coloured cells with both nuclear matrix and granules taking on the stain. (See Fig. 17). A proper appreciation of these histological types is necessary, as the faintly staining cells described under type I or the perinuclear spaces might readily be mistaken as examples of the earlier stages of chromatolysis, while the deeply staining type may be improperly regarded as showing pathological pigmentation.

In the experimental monkeys the posterior-root ganglion cells were involved in chromatolytic changes varying in degree and intensity. The earliest stage consists in swelling of the cell with disappaarance of the Nissl granules from a circumscribed peripheral area. This focal chromatolysis spreads centralwards, the nucleus, pari passu, is gradually displaced towards the opposite pole of the cell

and ultimately lies at the periphery, bulging outwards as if being extruded. The granules are now no longer distinguishable, the cell groundwork staining but faintly and studded with fine dust-like material. The final stage appears to be one of phagocytic removal of the cell-debris, as in some preparations the remains of disintegrated ganglion cells were seen in the midst of clusters of cells derived by proliferation from the surrounding neuroglia.

Where active substances were given hypodermically or by stomach-tube, a relatively acute phase was seen, characterised by cell death with either oedematous swelling or cell shrinkage, and nuclear disintegration with chromatolysis.

In the sympathetic system the lumbar ganglia were not much affected but in the superior cervical and stellate ganglia, vacuolation, chromatolysis, and displacement of nuclei were well marked in cases of acute poisoning. There was some correlation in the more chronic types between the severity of the clinical symptoms of inco-ordination, contracture, and wasting, ~~with~~ *and* the degree of pathological change found in the sympathetic ganglia. In one monkey fed on oats, there was proliferation of neuroglial cells with, in some areas, the suggestion of commencing fibrosis.

A preliminary study was made of the normal multipolar

Fig. 19. Spinal cord. Thionin. High power.
Multipolar nerve cells.
Chromatolysis, nuclear displacement.

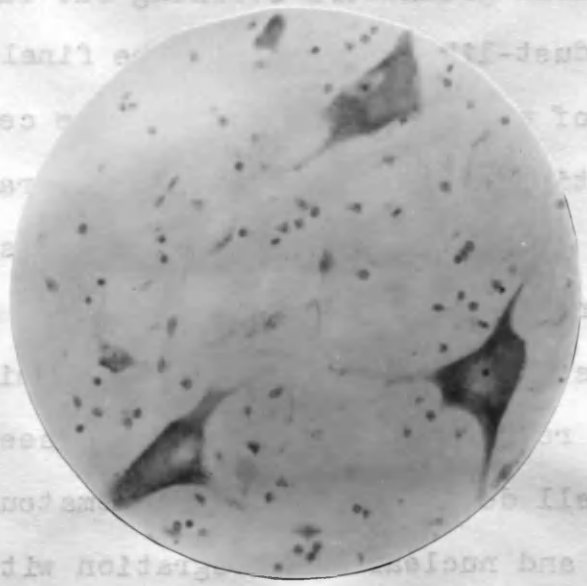
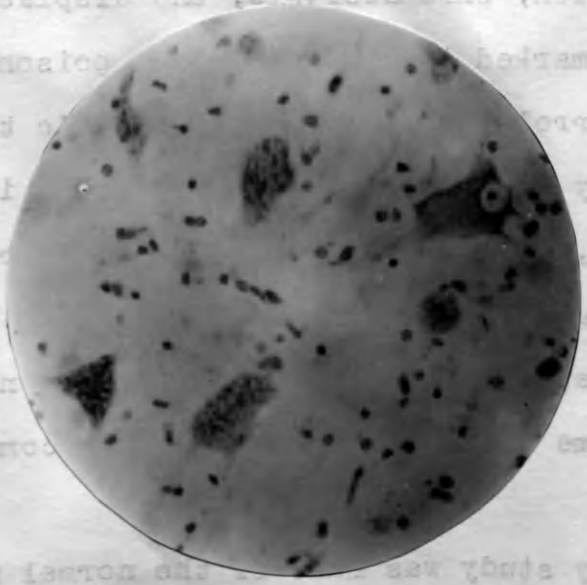


Fig.20. Spinal cord. Thionin. High power.
Multipolar nerve cell showing "extrusion" of nucleus.



nerve-cells in both rabbits and monkeys. With the technique adopted, the Nissl bodies appear as large, angular, deeply-staining granules, lying in a colourless matrix, the nucleus round and achromatic, the nucleolus rich in chromatin, and the perinuclear space clearly defined. The granules extend into the dendrites but the axon is pale and homogeneous.

In acute cases of poisoning, some of the large cells of the anterior horn - especially in the lumbar enlargements - showed partial or complete chromatolysis with eccentric displacement of the nucleus, which looked as if it were being extruded (Figure 20). Associated with the cellular changes there was not infrequently engorgement of the intercellular capillaries with minute haemorrhages. In the monkey poisoned by a massive dose of wheat extract (vide supra p. 19) the picture was that of acute oedema, vascular engorgement, and extravasation. The nerve cells were greatly distended while a few were shrunken and apparently bathed in fluid exudate.

In the feeding experiments, where the paralysis was more gradual in onset, a series of striking and constant changes occurred analagous to those noted in the root-ganglion cells. The dorsolateral column of Clarke was always affected. The change is first evidenced in the perinuclear region as a pale annular area surrounded by fragmentary granules, the nucleus oval or reniform and

faintly staining. All gradations are met with, the extreme being a swollen pale-staining cell with an ill-defined displaced nucleus and vacuolated cytoplasm.

Similar degenerative changes were found in the medullary and thalamic nuclei but the Purkinje cells of the cerebellum in the cases examined were apparently unaffected. In the acutely toxic animals the pyramidal cells of the motor cortex were damaged.

General Discussion:

The changes found in the viscera and the effects upon the nervous system lead one to conclude that we are dealing with a general intoxication. The visceral changes which I have described are of secondary importance but nevertheless play their part in the pathological story of cereal food poisoning. If a poisonous cereal or its active substance be taken per os, its absorption tends to evoke a response in the liver proportionate to the amount and concentration of the poison present. This response may vary from the slight vascular dilatation seen in the maize-fed monkeys to the necrosis observed in the case of acute wheat poisoning. Similarly it would seem that ordinarily the poisonous substance is detoxicated, but the renal epithelium is very susceptible to the undetoxicated material.

The nervous system is particularly vulnerable to cereal poisons. Where, for example, maize is consumed in

fair quantities over a long period of time, the active acid substance is not rendered wholly inert and exerts a harmful effect upon the neuronal tissues. The condition is one of intoxication and not of inflammation, the absence of inflammatory leucocytic reaction being a striking feature of the pathology. In my opinion, the protean character of the changes in the soft tissues is explained readily and logically by ascribing the lesions to a trophoneurosis. The paresis, the somnolence, the muscle atrophy, the skin lesions, are all clinical manifestations of interference with the trophic function of the cerebrospinal and autonomic systems.

In the early stages the damage to the nerve cells results in merely functional derangement with transient peripheral effects, but eventually a degree of trophic disturbance ensues which is evidenced clinically by persistent paresis and slight contractures, and pathologically by myelin degeneration and a more advanced cellular change. The final picture is that of cell destruction with irreparable damage to the associated nerve fibres.

In acute stages the cellular changes in the ganglia, cord and brain are greatly in excess of the amount of demonstrable myelin degeneration (which may, in fact, be absent) but in the more chronic and progressive types the reverse is true. There can be no doubt that the cell

change and the myelin degeneration are inter-related, but the question arises as to which precedes the other.

It is difficult to believe that such a highly specialised and delicate structure as a bipolar or multipolar nerve cell can be more immune to the poisons we are considering than a medullated nerve sheath. In acutely fatal cases there may be widespread cell damage with no apparent myelin change, and on the other hand, among animals but slightly affected or which have recovered, there are instances of early myelin degeneration with apparently normal nerve cells. From a study of the clinical effects of the active principles of maize, oats, etc. and the correlated pathological findings, I have concluded that all myelin change has been preceded by toxic injury to the cells. Except when the nervous system is "drenched" with a massive dose, the active principles of these cereals do not ordinarily produce cell death, but are capable of so damaging the ganglionic and multipolar nerve cells that the neuronal disturbance is demonstrated objectively by drowsiness, paresis, and general weakness, and pathologically by chromatolysis. The effect upon the cells, portrayed and measured by the chromatolysis and nuclear changes, may be recovered from and the histological appearances return to normal, but the trophic disturbance may have sufficiently affected the neurone that the myelin sheath, if not

permanently injured, takes time to recover and for a further period may show the Marchi degeneration. It cannot be too strongly insisted upon that we are not dealing with a "neuritis" but with a toxic cellular degeneration.

VI. A REVIEW of PREVIOUS EXPERIMENTAL WORK on ANIMALS and MAN

Pellagra and beri-beri have been experimentally reproduced in man in all their clinical manifestations. On the other hand there is no single instance where either has been faithfully reproduced under experimental conditions in all the essentials of clinical and pathological detail. I shall endeavour to demonstrate later that the preponderance of certain cereals in the diet may give rise to a common pathology although the clinical evidences may not correspond so closely. When it is appreciated that apparently discrepant variations in signs and symptoms can have a common pathological basis and, conversely, that superficially similar clinical conditions may have no real connection, a great deal of misconception and confusion with regard to "deficiency" diseases will be removed. In animal experiments care must be exercised in the interpretation of results, especially when the effects in one species are to be applied to another. For example, we find that changes produced by diet in rats and guineapigs are forthwith translated in terms of human pathology as if what may be induced in one of the lower animals must of necessity occur in man. Especially in feeding experiments it should be fundamental that the normal habits and requirements of the species of animal employed should be appreciated.

It may be stated generally that graminivorous birds thrive on whole grain but tend to develop polyneuritis when fed on milled grain, while mammals, with the exception of the omnivorous rat, are highly susceptible to staple cereal diets. In the present experiments with cereals, the results obtained varied greatly in rabbits and guineapigs, animals which under normal laboratory conditions consume a fair amount of cereals, but the reactions of monkeys were clear and decisive, the pathological changes approximating most closely to those found in fatal cases of human pellagra.

I have made a detailed study of the literature dealing with experiments in relation to the toxic effects of oats, wheat, rye, maize and rice. The following account, while not complete, may be regarded as representative of the recorded results in guineapigs, rabbits, mice, rats, fowls and pigeons, dogs, monkeys, and the few available experiments on man.

GUINEAPIGS.

Rondoni (1919):- In guineapigs fed on maize, death occurred on an average within 18 days, and changes were found in the nervous system, spleen, thyroid, and suprarenal glands. The spleen showed sclerotic lesions with diminution in the number of lymphocytes in the follicles. In the early stages there was hyperaemia of the thyroid gland with some epithelial proliferation followed by sclerosis.

The cortical cells of the suprarenal glands were degenerated and the chromaffin tissue stained poorly with chromium salts. There was some "decay in the anterior horn cells and in the Purkinje cells of the cerebellum..... and frequent irregular degeneration of medullated nerve fibres."

Rondoni, carrying his investigations further, found no difference in results by adding to the maize diet such substances as casein, peptone, tyrosine, and tryptophane. The addition of 10 grm. of cabbage prolonged the average life to 25 days, and the guineapigs only lost weight in the last few days before death. (Sandwith [1915] had independently made similar observations as to the effects of cabbage). Alcoholic extracts of maize bran did not help, but acid-alcohol extracts of cabbage had effects similar to the fresh vegetable. Alcoholic extracts of fresh guineapig liver prolonged life for a little.

The maize used (Italian) in these experiments must have been very poisonous to produce death in from 18 days to 25 days. In our feeding experiments only a proportion of the animals were affected and none died.

Karczag (1926). In two series of experiments with a staple maize diet the guineapigs developed gastrointestinal catarrh, with loss of hair and paralysis of the hind legs. In the second series these results were found to be

independent of whether the animals were kept in darkness or in daylight. Karczag described parenchymatous and pigmentary changes in the liver, spleen, and suprarenal glands but unfortunately did not examine the nervous system.

Holst & Fröhlich (1912) have repeatedly made the observation that the symptoms induced in guinea-pigs by exclusive diets of barley, oats, rice, and maize, resemble those of scurvy and that antiscorbutics such as green vegetables prevent or cure the condition. The guinea-pigs died invariably with 15 to 46 days. Only two developed polyneuritis, but all showed degeneration of the finer ramifications of the peripheral nerves. These opinions are not so irreconcilable with the views of Rondoni (supra), who speaks in terms of pellagra, when it is remembered that experimental scurvy, pellagra, and beri-beri, have some similar clinical manifestations and comparable histological changes.

RABBITS.

As I have already indicated (p.21.) rabbits vary greatly on a cereal diet, but a certain proportion show signs of poisoning with emaciation, loss of hair, paralysis, and decalcification of bone. Funk (1916) produced an acidosis in rabbits by feeding exclusively on oats, and according to Schaumann (1914) maize causes polyneuritis.

RATS.

Holst & Fröhlich (1912) stated that rats remain healthy on maize but Nicolls (1913), using a staple diet of soured maize, found loss of hair, ataxic gait, with haemorrhages and degenerative changes in the liver and spleen. Morgen and Beger (1915) fed rats on a diet composed wholly of oats. They were unable to keep the animals alive for more than a few months, but found that sodium bicarbonate maintained the rats in good condition. Their conclusion that the condition was an acidosis was upheld by Funk (1916) who claimed to have substantiated their results.

Chick & Roscoe (1928) produced a condition in rats characterised by lack of growth, loss of hair, and symmetrical dermatitis affecting the ears and digits. This they termed "rat pellagra". The diet was composed of caseinogen, cotton seed oil, salt mixture, and 60% rice starch, a combination held to be deficient in vitamin B_2, identical with the pellagra-preventing factor of Goldberger. Stern and Findlay (1929) using a similar combination with 70% rice starch and a daily allowance per rat of 0.2 grm. cod-liver oil, reported lipochrome pigmentation of the multipolar nerve cells in the spinal cord. Neither their account of the clinical appearances nor their microphotographs give grounds for assuming the analogy to pellagra.

Kollath (1929), in an excellent paper, holds that there is no proof of the identity of human and rat pellagra, an attitude which is amply justified on a critical examination of the pathological findings. Using a feeding mixture similar to Chick & Roscoe, but with 65%-70% rice starch and cod-liver oil, Woollard (1927) & Findlay (1928) induced changes viewed by the latter as a typical polyneuritis and by the former as consisting merely of structural alterations in the intermuscular medullated motor and sensory nerve endings.

I have compiled the following comparative table from the papers by the authors indicated. The formulae were used as basal diets in their experiments on rats for the production of vitamin deficiency disease and also in the testing of the vitamin content of foodstuffs.

TABLE

	Vitamin deficient	Rice starch	Caseinogen.	Vegetable oil	Salt mixture
Chick & Hume 1927	B	63	21	11	5
Do. do. 1929	B_1	60	20	15	5
Aykroyd & Roscoe 1928	B_2	60	20	15	5
Findlay 1928	B_1 & B_2	70	25	-	5
Woollard 1927	B_2	65	20	10	5

The outstanding feature of these very similar diets is the high proportion of cereal present. In the emphasis laid upon the vitamins absent from or subsequently added to the diets, the cereal content, and the possibility of this playing an active part in such conditions as "rat pellagra" and polyneuritis, has been ignored.

MICE.

Horbaczewski fed mice on boiled yellow maize, with and without milk. While ordinary mice thrived, albinos developed "pellagra", due, he believed, to a fluorescent alcohol-soluble colouring matter in the maize which induced special sensitivity to direct sunlight. Raubitschek (1912) claimed to confirm this reaction in albino mice and, from the effects of feeding and injecting alcoholic extracts of maize in guinea-pigs, concluded he had produced pellagra by a photosensitising substance. These assumptions were definitely negatived by Hirschfelder (1912) who pointed out that white maize, containing no fluorescent colouring matter, was equally pellagrogenic.

PIGEONS AND FOWLS.

These graminivorous birds thrive on unhusked maize (Schaumann 1914), whole wheat (Hart, Halpin, & McCollum 1917) and unhulled rice (Gibson 1913). With finely milled cereals, especially rice, a polyneuritis ensues which, in

most cases, may be recovered from by the administration of rice polishings or extracts thereof. Gibson observed that the administration of the lactate and other salts of calcium prolonged the period required for the development of neuritis, and that fowls so fed developed brilliant combs and fine plumage in contrast to the other experimental birds deprived of such additional calcium. The condition has been ascribed to the lack of an antineuritic vitamin (B or B_1). Distinctions have been drawn between "polyneuritis columbarum" and "beri-beri columbarum", the latter term being confined to the disease in pigeons which shows oedema and cardiac enlargement in addition to polyneuritis (Graham 1927, McCarrison 1928). A full account of the histological changes in the nervous system is furnished by Findlay (1921) who found irregularly scattered myelin change in the peripheral nerves, spinal cord and brain. This author describes chromatolytic and nuclear degeneration of the motor cells of the cord which he holds are common to human and avian beri-beri, although much more pronounced in man.

It is questionable whether avian polyneuritis is a true neuritis. Pigeons with a degree of paralysis which might suggest gross damage to nerve fibres may recover with dramatic rapidity after the administration of rice polishings. Conversely, degeneration may occur before symptoms are apparent during life, and Vedder (1918) therefore held

that a peripheral neuritis is not the essential lesion. Cooper (1912) denied that there is any demonstrable connection between the intensity of paralysis and the degree of nerve degeneration. Kon and Drummond (1927) give the opinion that the prompt alleviation of the acute nervous symptoms proves the absence of true nerve change but, on the other hand, the paralytic form of polyneuritis columbarum is incurable and is definitely associated with nerve degeneration. On consideration of the evidence one agrees that this view is borne out by the facts, and for the present discussion, the salient feature of paralytic experimental polyneuritis in birds is the constant association of myelin degeneration and nerve-cell chromatolysis with an exclusive diet of milled cereal.

PIGS.

Weiser (1912) noted that pigs fed on maize perish from malnutrition. Polyneuritis with typical myelin degeneration has been found in pigs fed on large quantities of hulled rice, cotton seed meal and maize (Rommel & Vedder 1915), and maize in the form of corn-tankage (Hughes et. al. 1929). Hart, Miller and McCollum (1916), in a much quoted paper, concluded that a large proportion of wheat in the diet produced toxicity manifesting itself by neurological changes not unlike beri-beri, and that "no one important

factor such as better protein, salts, or vitamin A appears able to act as a corrective for this toxicity." The pigs developed stiffness, weakness, and inco-ordination of movement which were correlated with histological changes in the lower regions of the spinal cord. The motor cells were compressed and bathed in fluid, their processes partly degenerated, and the nuclei shrunken.

Hughes, Lienhardt and Aubel (1929, ut supra) found scattered myelin degeneration in the optic, femoral, and sciatic nerves, in certain parts of the spinal cord and in the optic thalamus. This paper is furnished with excellent microphotographs which resemble plate 13 (p.42a).

DOGS.

Chittenden & Underhill (1917) fed dogs for several weeks and months on a diet composed of wheat flour, boiled peas, and vegetable oil (cottonseed or linseed). The experiment was repeated with white bread, lard, and milk, and when fresh meat was added early enough, a cure resulted. This diet has been criticised as containing low-grade protein, poor salt balance, and as being deficient in vitamins A. and B. (McCollum et al. 1918). The animals developed anorexia, diarrhoea, ulceration of the mucous membrane of the mouth, and pustular skin lesions on the thorax and abdomen. The condition was termed "experimental black-

tongue" and has been held as analogous to pellagra. Denton (1928) investigated the tissue changes. The lesions of the buccal mucosa and of the corium of the skin begin as a degenerative process of the superficial layers, followed by secondary fibrotic changes, with a tendency to terminate in extensive necrotic inflammation. No changes were found in the nervous system or in any other organ. It is difficult to see how such lesions, occurring apart from any nervous or visceral changes, should be specially correlated with those of pellagrous origin, and yet experimental black-tongue has been adduced as one of the strong links in the chain of evidence to prove that pellagra is an avitaminotic disease.

Using an artificial diet (casein, rice or maize starch, etc.) to investigate the effect on dogs of "water-soluble B deficiency", Zimmerman & Burack (1932) found extensive myelin degeneration in the peripheral nerves of all the animals tested, with early chromatolytic changes in the brain and spinal cord. The extent of the anatomical alterations in the peripheral nerves varied in direct proportion to the severity and duration of the paralytic symptoms found during life. The myelin destruction was most severe in the sciatic and least severe in the vagus nerves of all the animals.

Mellanby (1931) fed young puppies on diets rich in cereals. The basal diet consisted of white flour with lean meat, olive oil, yeast, orange juice and separated milk. The age of the puppies at the commencement ranged from six to ten weeks. Although some litters were found to be remarkably resistant, the affected animals after 2-3 months developed symptoms of inco-ordination of movement, and post-mortem examination showed a diffusely scattered myelin degeneration in the anterior and posterior columns and cerebellar tracts of the spinal cord. Substitution in whole or in part of the white flour by wheat embryo, rye, or white maize intensified the symptoms and the degeneration. A supply of vitamin A or of carotene prevented the nervous changes, while 2-5 gram. ergot increased the degree and extent of the myelin degeneration. Mellanby, forced to the conclusion that mere deficiency of vitamin A does not sufficiently explain the facts, assumed that the cereals contain a neurotoxin whose effects can be prevented by vitamin A and he connected his findings and hypothesis with pellagra and convulsive ergotism.

Commenting on his work, he remarks (1933): "Of all the cereals tested one stands out as an exception to the general rule, viz., yellow maize..... With yellow maize the cord is normal. The anomalous position of yellow maize is due, no doubt, to the protective action of its yellow

pigment, carotene...." With this statement I emphatically disagree. Stockman and myself used yellow maize both for feeding purposes and as a source of the active principle, consistently obtaining severe nervous system degeneration in monkeys and producing symptoms in several rabbits. One cannot help thinking that Mellanby marred his deductions by having a fixed conclusion in view, but his insistence upon the relative harmlessness of yellow maize is inexplicable. The changes produced in his affected puppies are similar to but much less intense than those recorded in our experiments. The explanation would appear to be that Mellanby used a correspondingly smaller amount of cereal (10% of total diet). It should be noted that he began with the conception of a vitamin deficiency which in reality he tends to stress rather than the nature and amount of cereal present.

MONKEYS.

The number of recorded experiments with cereals on monkeys appears to be small.

Schaumann (1910):- A monkey fed on rice lost appetite and developed paralysis of the lower extremities with progressive marasmus. Many nerve fibres were found to be degenerated. The record of the experiment is meagre and histological minutiae are omitted. Aron (1910), quoted by Gibson, obtained a similar result in three monkeys

fed on white bread.

Shiga and Kusama (1911):- One monkey fed on rice developed a voracious appetite at the beginning of the experiment. On the 37th day the animal was disinclined for food and the pateller reflex was abolished. Paralysis of the lower limbs rapidly set in and death occurred on the 47th day. The heart was dilated and the skeletal muscles atrophic. The peripheral nerves had scattered degeneration of the medullated sheath and the motor nerve cells of the spinal cord showed absence of the Nissl granules.

Gibson (1913):- Boiled rice was fed to six monkeys, three of which had salt mixture (Osborne & Mendel) in addition. One salt-fed monkey developed oedema on the 43rd day and died on the 46th day. The sciatic nerve showed Wallerian degeneration. Another monkey, fed on rice only, lost condition, dying on the 86th day. (No report is given of the histological examination). The experiment was discontinued on the 120th day as the remainder were unaffected.

Koch & Voegtlin (1916). One Rhesus monkey in good health and fed on a liberal mixed diet was used as a control, killed under chloroform, and found on detailed examination to show no pathological lesions. Another monkey existed for 175 days on raw carrots ad libitum, becoming extremely emaciated, but showed no pathological changes apart from congestion of liver, spleen and kidney. Monkeys

I and II were, restricted to 100 grm. per diem of corn-oil cake, corresponding to the type used in my experiment. IV and V were fed entirely on yellow maize meal while III received equal parts of maize meal and sweet potatoes. Those fed on maize cake died in 61 days and 78 days respectively, those on yellow maize in 54 days and 52 days, and the one on maize and sweet potato lived for 49 days. All were depressed or stuporose before death and much emaciated, with congestion and toxic cellular degeneration of the liver, spleen, kidney, and gastro-intestinal tract. No section from the central nervous system in I (maize cake) was examined. In II (maize cake) diffuse myelin degeneration occurred in the dorsal region of the spinal cord, in IV and V (yellow maize) the posterior columns were involved, but in III (maize and potato) no change was found.

These experiments of Koch and Voegtlin closely resemble those of Stockman and myself and the detailed microscopical changes in the viscera are similar to those in my sections, but unfortunately the neuropathology was not fully investigated.

EXPERIMENTS ON HUMAN BEINGS.

Volpino et al. (1912) observed that neither healthy nor pellagrous persons reacted to aqueous extracts of damaged maize administered by mouth. On the other hand,

in 12 out of 13 pellagrins tested, hypodermic injection of 1-2 c.c. of these extracts induced symptoms of central nervous disorder accompanied by rise of temperature. Healthy men and animals gave no such reaction. The active principle of the maize extract, termed "pellagrogenin", was soluble in water, resisted heating to 115° C. and could be precipitated by alcohol. Volpino and his co-workers were unable to demonstrate the existence of specific antibodies by serological methods and concluded that the active substance was not a true toxin. Rondoni (1912) repeated the experiment with extracts of healthy and of unsound maize, but found some rise in temperature even in healthy persons although the reaction in pellagrins was more marked. He could not decide whether the toxin existed originally in maize or whether it was formed only after the grain was damaged by fermentation or by putrefaction.

Goldberger (1916) conducted a unique experiment. Eleven convicts, (who volunteered on the promise of a free pardon) were restricted to a diet prepared from wheat flour, maize, polished rice, sugar, molasses, sweet potatoes, pork fat, green vegetables and coffee. The experiment began on April 19, 1915 and continued until October 31, 1915, a period of 5½ months, by which time 6 of the 11 men showed skin lesions symptomatic of incipient pellagra, a diagnosis confirmed by several dermatologists familiar with the disease.

On the strength of these observations Goldberger prophesied that "pellagra will prove to be a deficiency disease very closely related to beri-beri." McCollum & Simmonds (1917) pointed out that the diet employed by Goldberger contains 96% of total solids derived from maize, wheat, rice, sugars and pork fat.

Stannus (1913):- Native prisoners in Nyassaland were fed on a regulation diet of 1½ lbs. decorticated rice per diem with an allowance of salt. Four of the affected men had maize in addition. 31 prisoners developed typical pellagra, with mental depression, muscular weakness in the lower limbs, and finally a paraplegia, flaccid or spastic. The pellagrous rash appeared not only on exposed areas but also in the scrotum. No case of pellagra developed among the warders or the prisoners' wives who received a mixed diet of rice, maize, fish, beans, and green foods.

While in Goldberger's convicts the sole manifestations of the disease were in the skin, the Nyassaland prisoners presented the composite picture of fully established pellagra with both skin and nervous symptoms. It should be noted that the diet which produced unmistakable pellagra in Nyassaland is of the same type as that which produces beri-beri in Asia.

VII. PELLAGRA

Historical:

The first authentic description of pellagra is that of a Spanish physician, Gaspar Casal, who observed it among the peasants of the Asturias in 1735. His work, which was written in Latin and published posthumously by Joseph Garcia in 1762, contains a picturesque clinical account of this disease in crisp language exemplified by his note on the cutaneous lesion:- "Degenerat tandem in crustam sicissimam, scabrosam, nigricantem, profundis saepissime intercissam fissuris....." The disease was noted in Italy (1740) by Professor Guiseppe Pujati and in 1771 Franceso Frapolli described it as "pellagra" (rough skin) by which name it had long been known to the peasantry of Lombardy. It was found in North & Central Italy, among the foothills of the Alps and of the Apennines, the same localities where it is now indigenous. In Lombardy alone, from 1770 to 1880, the number of known pellagrosi increased from 20,000 to 104,000 and in 1910, in North & Central Italy with a population of 16,600,000 it was estimated that five per cent. of the inhabitants were affected. In France, Jean Hameau (1818) found it in the Landes of Gascony but it has diminished in this area since 1890 consequent upon improvements of food and the introduction of

relatively better standards of living. Sporadic cases had been noted in the United States of America since the middle of the nineteenth century, but in 1907 Babcock & Watson drew attention to the alarming spread of pellagra throughout the country, and within three or four years it prevailed in 33 States with no less than 10,000 indubitable cases on record. Wood (1920) has made the interesting observation that from 1905 to 1909 he encountered a malignant and fulminating type of disease but in 1920 recorded that it had become chronic in nature, differing little from the Italian type. In Great Britain the few cases reported have been mostly inmates of Asylums.

It is of strange significance that the endemic or epidemic appearance of the disease in any area has in most instances followed the introduction of maize as an important article of diet in the community, although it will be noted later that pellagra is not solely associated with maize. The progress of the malady can be traced from Spain to Southern France, North and Central Italy, Upper Egypt and other parts of Africa, Austria, the Balkans, Asia Minor, India, Mexico, Barbadoes and parts of North and South America. Many local names have been applied to the disease, most of which have a bearing upon the popular ideas of etiology, viz., Mal de la Rosa, Risipolo Lombardo (Lombardy Erysipelas), Lepra Italica, Alpine Scurvy, Mal Rosso,

Maïdica, Mal de Sole, Mal de Asturias, Mal de la misère, etc., but the term "Pellagra" is now standard in literature. The clinical syndrome of pellagra has been summarised as "Dermatitis, Diarrhoea and Depression," but I have heard a not less apt alliteration from an Italian friend which, translated into English, describes the association of the disease as "Peasant-life, Poverty, Polenta (maize), Pellagra."

Clinical Features of Pellagra:

While one typical feature of pellagra is its chronicity, there are records of an acute form, the so-called "typhus pellagrosus", manifested by pyrexia and the typhoid state. The intelligence is clouded at an early stage followed rapidly by delirium. There is hypertonicity of the whole muscular system, sometimes so marked as to cause opisthotonus and, with the onset of pneumonia, encephalitis or some other complication, death ensues in 1-2 weeks.

Ordinarily the development of the disease is progressive and as a rule the illness lasts for decades, although the cachexia or the supervening nervous and mental disturbance may terminate the picture within a period of months or a few years. The early history is one of slight attacks recurring in spring and autumn. In the attacks there is a peculiar awkwardness of movement which makes the gait typically cumbrous. There may be headaches and dizziness,

sleeplessness, general weakness, paraesthesias and neuralgias. The appetite is poor and there is generally gastro-intestinal disorder. The attacks recur year after year and gradually there appears a group of serious nervous disturbances most commonly manifested by paralysis and tonic or clonic spasms, the knee jerks being exaggerated or absent. Vertigo, tremors, and twitchings, or even epileptiform seizures, are common while the gait is that of spastic paraplegia. The cranial nerves may be affected, and severe neuralgias and obstinate paraesthesias of the most multiform character contribute to the development of mental disturbance. The mental picture may range from mere apathy and amnesia to a state simulating paralytic dementia. The pellagrous rash, which gave the name to the disease, affects those parts exposed to light and notably to direct sunlight, and Stannus (1913) records cases from Tanganyika where the scrotum was involved, presumably by irritation. It appears as a remarkably symmetrical erythema, light red, dark red, or bluish in tint, accompanied by a burning sensation which at times may be almost intolerable. The dermatitis may become vesicular or pustular. After repeated attacks hyperkeratosis with desquamation sets in, the skin is dry, pigmented and parchment-like, and ultimately becomes shrunken, wrinkled, and atrophic. On occasion the exanthem has been confined to scaliness and, especially in America (Roberts

1920), many cases of unmistakable pellagra were found with no eruption, a condition known as "pellagra sine pellagra", or, more properly, "pellagra sine exanthem."

It has long been recognised that in the early stages a complete change of diet, especially the use of meat, eggs, milk, fresh vegetables etc., effects a cure, but in the advanced cases the prognosis is exceedingly grave. The profound pathological changes occurring in the central nervous system, with records of which the literature abounds, explain the hopelessness of those cases where the typical widespread damage to the nerve cells and fibres has occurred.

Pathology:

Many and varied lesions have been described by numerous authors as occurring in or being typical of pellagra but a critical survey of the literature leads to the conclusion that the visceral changes are of secondary importance compared with the remarkably consistent findings in the nervous system. In cases coming to post mortem in the early or acute stages there is generally found a marked loss of adipose tissue, congestion of the whole gastro-intestinal tract passing on to atrophy (Wilson 1914, Drummond 1913), and a degenerative atrophy of liver, spleen, heart, kidney and muscles often associated with deposits of blood pigment (Wilson 1914, Bigland 1920, Susman 1930). A somewhat

modern observation is atrophy of the endocrine tissues, especially of the suprarenal gland (Bigland 1920, Boyd 1920, Roaf 1920). Susman (1930) found constant changes in the thyroid gland consisting of proliferation of the vesicular epithelium, interstitial fibrosis, and pigmentation. In the later stages, when the nervous and mental symptoms have appeared, there are extensive and diversified changes in the nervous system. The blood shows a mild anaemia with relative increase in lymphocytes. The skin at the site of the eruption shows atrophy of the stratum corneum, irregular cell proliferation of the rete mucosum, and sclerotic changes in the smaller blood vessels of the dermis (Nicolls 1913).

The Pathological Anatomy of the Central Nervous System in Pellagra:

Papers dealing systematically and thoroughly with the pathological anatomy of the central nervous system in pellagra are rare. Tuczek in a paper "Uber die nervösen Störungen bei der Pellagra" in 1888 and later in a monograph (1893) gave an accurate and detailed account of the neuropathology as known and demonstrable in his day, while of more recent date a publication of Singer & Pollák (1913) gives a comprehensive survey of the literature and an account of the histological minutiae of the nerve-cell changes. Among the several hundreds of published accounts

scrutinised, the earliest reference noted is that of Landouzy (1855) who reported microscopic findings of softening and sclerosis of the spinal cord. Tonnini (1883-84) found fatty degeneration of the anterior and posterior cornual cells and first described the degenerative changes in the lateral columns of the cord. Belmondo (1889) described an acute meningomyelitis as the pathological basis of the fulminating acute cases of pellagra and in the most chronic type a systematic combined postero-lateral sclerosis with pigmentary degeneration of the spinal and sympathetic ganglia. Tuczek (1893), in a classical monograph (Klinische and anatomische Studien über die Pellagra), discounted the hitherto accepted findings of inflammatory reactions in the meninges and concluded that "the most noteworthy and constant lesion, and one that may be taken as peculiar of the disorder is an affection of the spinal cord especially of its lateral columns." Marie (1894) and Lombroso (1898) confirmed these spinal cord lesions but it remained for Babes & Sion (1899) to describe the degenerative changes in the brain, particularly the chromatolysis in the cells of the cortex. Subsequent workers have merely confirmed or elaborated the observations of these pioneers.

There is common agreement among modern authors that in human pellagra there are two classes of well defined changes affecting the whole nervous system, centrally and peri-

pherally, the one evidenced in the nerve cells, the other in the medullated nerve fibres.

The language used by various writers in describing the cellular changes is monotonously similar. I shall quote here a British author (Watson 1921) to illustrate the typical phraseology, but also more especially to draw attention to the histological identity between the changes found in indubitable cases of pellagra and those observed in my sections from experimental monkeys and illustrated in this thesis (vide Figs. 19-20 p. 47a.). Watson, describing the microscopical findings in 21 fatal cases of pellagra occurring in Rainhill Asylum, Liverpool, states:-
"In the acute and sub-acute cases, and also in the severe chronic ones..... The cells are usually swollen and they show advanced chromatolysis, most of the stainable substance being at the periphery of the cell, sometimes at one side only. The nucleus is often swollen, but at times shrunken and distorted. It is usually displaced to one side, either about the middle of the cell, or nearer the base, or towards the apex, and is frequently partly extruded....." This change has been found in the large pyramidal cells of the cerebral cortex, the hippocampal region, the dentate nucleus of the cerebellum, the nuclei of the cranial nerves, Clarke's column and the anterior cornua of the spinal cord, the posterior root and sympathetic ganglia (Mott 1913, Singer

& Pollock 1914, Wilson 1914, Watson 1921, Winkelman 1926).

The nerve fibre lesion, excellently illustrated in a paper by Mott (1913), has been admirably summed up by Stannus (1912) as "a chronic pseudo-systematised degeneration affecting all portions of the nervous system, resembling the condition found in subacute combined degeneration of the cord....."

THE ETIOLOGY FROM PELLAGRA.

Much has been written on the etiology of pellagra, at least twenty-six different theories being found in the literature, many of which have been acknowledged by few except their authors. In view of the subsequent discussion (vide IX. p.91) directed to the correlation of pellagra with the present research, a mere outline will be given here of several hypotheses, somewhat crudely classified to show the variety of thought and change of outlook which has been brought to bear upon the subject. Investigators have occupied one of two divided camps, the "zeists" who believe that maize is the responsible factor, and the "anti-zeists" who at least agree in denying any special relationship between pellagra and maize. The Italian school have long been the great protagonists of the zeistic doctrine but since 1914 Cencelli and others have departed from their native traditional view to agree with those who stress the low nutritive value of maize.

The toxic zeïstic theory, associated especially with the name of Lombroso (1871), attributes pellagra to some toxic substance present in or produced from either sound or damaged maize. Toxins developed from the grain by moulds or by pathogenic contamination, and autointoxication resulting from a staple maize diet are causes zeïstic in essence by assuming maize to be a necessary although secondary factor.

Raubitschek (1912), from studies in the experimental production of pellagra, concluded that certain cereals (including maize) contain a substance which renders the skin sensitive to light, a statement upheld by Suarez (1916) who termed the photo-sensitising principle in maize "zeochin". This photo-dynamic theory arose from the conception that the skin lesions constitute the characteristic feature of pellagra and is based upon the reaction of white mice and guineapigs fed upon maize or maize extract while exposed to sunlight. The hypothesis received scant recognition, but quite recently Sabry (1932) has revived the basic idea of Raubitschek and Suarez. He identifies a toxic substance present in maize and other cereals with dioxyphenylalanine and he explains the dermatitis and pigmentation as a defence reaction, melanin being formed in the deeper layers of the dermis following the neutralisation of the circulating toxin by an intracellular oxidase.

Stannus (1913) had previously attributed the skin lesions to phytoporphyrin or haematoporphyrin present in the blood as the result of cereal diet (rice), but he did not stress the point as being of etiological importance.

It would appear inevitable that infection should have been invoked to explain pellagra. Sambon (1913) so successfully propounded the theory of a protozoal infection, transmitted by a blood-sucking insect (Simulium) which breeds in water, that an English Commission was sent out under his leadership to make further investigations in the West Indies. In 1914 he incriminated the Chironomidae and Ceratopogoninae, insects whose habits and whose relationship to pellagra are equally unknown. Yet another insect, the Stomoxys calcitrans has been suspected as the carrier of pellagra from human to human (Siler et al. 1914). Fungi, a Streptobacillus pellagrae (recovered from the blood and faeces of pellagrins), and a Gram-positive coccus (obtained from "pellagrous" rats) have been described but not corroborated. Susman (1927) isolated an anaerobe from the blood of pellagrins, and concluded that the disease is a blood-borne infection which, through thyroid and metabolic disturbances, produces endogenous toxins capable of damaging the central nervous system, skin and kidneys. The advocates of the infective theory have based their case upon unsubstantiated evidence and unwarranted assumptions, and

there is now general agreement that infection per se is of no etiological importance. Goldberger (1916) investigating the transmissibility of pellagra, found that blood, urine, faeces, scales from skin lesions, and the nasopharyngeal secretions of pellagrous patients could not transmit the disease to healthy human beings.

I have been able to find in the literature but one "chemical" theory. Alessandrini and Scala (1916) attributed pellagra to the consumption in the drinking water of colloidal silicic acid and the Pellagra Commission of Rome went the length of purifying the water supplies of certain endemic areas.

From its earliest recognition pellagra has been associated with diet, but during the past twenty years there has been a steady departure from the doctrine of the Zeïsts to the other extreme of seeking the cause in the absence of some essential component, or components, from the dietary of pellagrins. Osborne & Mendel (1912) pointed out that maize protein (zëin) is inadequate for the promotion and maintenance of growth in experimental animals, owing, as they believed, to the absence of tryptophane and lysine. Goldberger (1916), after feeding experiments upon convicts, held that pellagra results from a diet deficient in protein both as regards quality and quantity. In his view the pellagrogenic diet has a low content of animal and leguminous

protein with a relative preponderance of non-leguminous vegetable protein. The findings of Goldberger and his colleagues were favourably received and resulted in a spate of research, especially in America, directed to the nature of the dietary deficiency (Voegtlin 1915, Koch and Voegtlin 1916, Hunter et al. 1916, etc.) Wilson (1919) laid emphasis upon the low biological value of the protein intake.

In 1920 two papers challenged Goldberger's hypothesis. Enright, (1920) reporting upon the pellagra outbreak among German and Turkish prisoners in Egypt, recorded that the German pellagrins had a diet ample both in quality and quantity, a statement which Goldberger (1920) sought to explain away by the suggestion that improper distribution of rations and individual eccentricities of taste accounted for the small proportion of German cases. Viswalingam (1920) studied pellagra in the Malay States among Chinese coolies who ate no maize but existed on polished rice, fish, pork, potatoes and green vegetables. He considered that a faulty diet cannot cause pellagra without a superadded microbic infection. Goldberger and Tanner (1922) narrowed the issue by announcing that the essential etiological factor is a specific defect in the amino-acid supply, "probably..... a deficiency of some special combination of amino-acids" to which conclusion they added (1924)

"..... a deficiency in some as yet unrecognised dietary complex, possibly a vitamin."

As far back as 1914 Funk, in a paper "Prophylaxie und Therapie der Pellagra in Licht der Vitaminlehre", declared that the milling of maize rendered the grain deficient in vitamins and so predisposed to pellagra, a view upheld by Vedder (1916) and Wood (1916). As the role of vitamin deficiency in nutritional disorders grew in popularity, experimental work in the production of pellagra or pellagroid conditions in animals contributed more weight to the assumption that pellagra follows a deficiency of vitamins A and B, singly or together. Goldberger and his co-workers (1925), (1926), finally declared that the disease is caused by deficiency of a pellagra-preventing (P-P) factor which, though similar to vitamin B, is distinct from the anti-neuritic principle. The pellagra-preventing factor (the vitamin B_2 of English authors) they hold to be both prophylactic and curative, cure being assessed by the effect produced upon pellagrous skin lesions.

Mellanby (1931) (vide antea p.63), finding that Goldberger's hypothesis does not wholly meet the facts, has postulated a neurotoxin (or 'toxamin') in certain cereals, and suggests that in pellagra there is a double deficiency, lack of vitamin B_2 producing the skin lesions, and absence of vitamin A allowing the nerve degeneration to develop through the action of the toxamin.

VIII. B E R I - B E R I

As pellagra with maize, so beri-beri has had a popular association with rice, a relationship which has been more closely defined since the epoch-making researches of Eijkman (1897) into the connection between polished rice and beri-beri. It is apt to be forgotten that the disease is not a product of the age of machinery, but for centuries has been a recognised clinical entity, especially in the Orient. The name "beri-beri" is of Singalese origin and denotes "weakness", aptly describing the condition of the victims. Findlay (1917) states that Strabo (A.D. 2) mentions an epidemic among the Roman legionaries in Arabia in 24 B.C., and the annals of Chinese medicine of the second century contain full and accurate descriptions of the disease. Found as a comparative rarity in Europe (undoubted cases being found mainly in prisons and asylums), it is endemic in Japan, China, Malaya, the East Indies and Philippine Islands, Brazil and Africa. It has been found among the fishermen of Newfoundland and Labrador where rice is unknown and fine wheaten flour the staple dietary (Little 1912).

The clinical features of the disease are epitomised by Vedder (1913) in his monograph:- "Beri-beri is an acute or chronic disease characterised by changes in the nervous

system and particularly by a multiple peripheral neuritis with an especial tendency to attack the nerves of the limbs, the vagi and the phrenics. Ordinarily the clinical picture of a peripheral neuritis is combined in varying degrees with cardiac disturbances, oedema, serous effusion, and gastro-intestinal derangements. Exceptional cases occur in which cardiac dilatation and sudden death are the first symptoms observed." A disease among infants, suckled by mothers who live almost exclusively on rice, has been common in the Philippines and in Japan, which on clinical and pathological grounds has been termed "infantile beri-beri". It has been found in other regions, particularly in Central America, where rice is not the staple diet or is even unknown. This form approximates to the acute fatal type of beri-beri as found among adults. Some would relate nutritional oedema with beri-beri, but there appears to be no grounds for this.

I would point out at this juncture that the commonly accepted view, expressed in the above quotation from Vedder, of a peripheral neuritis as the basis of the disease is not borne out by a study of the clinical manifestations. The acute cases clearly present the symptoms of an acute intoxication which may be followed by death within 24 hours after the appearance of the first symptom. The more chronic forms are ushered in by vague general prodromal symptoms

followed by signs of nervous involvement of significantly symmetrical distribution. The sensory disturbances (parasthesia, anaesthesia) and the paresis do not correspond to the anatomical course of the peripheral nerves, but are always segmental in distribution and ascending in order of appearance according to the successive levels of the spinal cord involved. The paresis of the bladder, commented upon by many authors as an early symptom, the hypertonus of muscle with exaggerated reflexes, followed by corresponding depression or abolition of reflexes and muscle wasting, all point to a spinal condition suggestive of a myelitis rather than a neuritis, a view which is borne out by the pathological findings.

THE PATHOLOGY OF BERI-BERI

In a critical examination of the literature on the subject, one finds so much confusion between human beri-beri and experimental polyneuritis that it is difficult to find an accurate and coherent account of the pathological changes found in man. Several otherwise valuable papers fail to give sufficient detail in one or other vital point, while many contain merely a brief description of peripheral nerve changes with no reference to the examination of the brain and spinal cord.

The recorded visceral changes are few. In acute fatal cases the mucosa of stomach, duodenum, and upper jejunum, with the related mesenteric lymph glands, are more or less acutely congested with occasional minute haemorrhages, a condition first described by Ellis (1898). In the sub-acute and chronic types there is chronic venous congestion of the liver, spleen, kidneys, and the upper portions of the gastrointestinal tract, changes which are typically wanting in polyneuritis columbarum (McCarrison 1918, 1919). It is commonly stated that the heart shows no demonstrable anatomical change but recent workers have described degeneration of the intracardiac nerve bundles (Bernard & Bablet 1927). In fatal cases of some duration the skeletal muscles show loss of cross-striation, softening of the fibres with accumulation of fat droplets beneath the sarcolemmal sheath, and proliferation of nuclei.

The nervous system shows changes affecting the spinal cord, peripheral nerves, posterior root and sympathetic ganglia (Wright 1901, Vedder & Clark 1912, Vedder 1913). In recent, acute, cases Wright (1901) found swollen nerve cells with slight chromatolysis and displacement of the nuclei, involving the anterior horns and the columns of Clarke in every level of the cord. In the peripheral nerves there is degeneration of the myelin sheath, the axis cylinders not being involved until the later stages of

chronic cases. The fact that clinical recovery of nerve function can rapidly be restored in early cases militates against the existence of widespread axonal degeneration. The myelin degeneration of the peripheral fibres spreads centralwards with ultimate involvement of the cerebrospinal system. The anatomical changes found in the brain in pellagra have not been demonstrated in beri-beri, but with this exception, the two diseases present the same type of lesions in the spinal cord and peripheral nerves. In anticipation of later discussion I submit that pellagra and beri-beri are essentially similar conditions with a common pathological basis, differing only in the distribution of the changes, pellagra resulting from involvement of the upper regions of the cerebrospinal axis and beri-beri from the lower.

THE ETIOLOGY OF BERI-BERI

Beri-beri has been regarded by some as a specific infection and a variety of protozoal and bacterial causes have been adduced, including a staphylococcus (Hunter 1897) B. aesthogenes (Bernard 1923, Cannon 1929) B. mycoides, and B. mesentericus. Japanese workers have held that cultures of Streptococcus sakè can produce the disease and that a vaccine thereof is of great therapeutic value. A team of Japanese investigators (Matsumura et al. 1929) has recently

challenged the importance of rice as the primary factor in beri-beri. They claim to have isolated a Bacillus beri-beri from the faeces of affected human beings which, when fed to pigeons, produces typical polyneuritis columbarum. The sera of infected birds and of sufferers from human beri-beri were found to contain potent specific agglutins for this bacillus.

The association of rice with beri-beri has been so clearly recognised that the cause has long been sought for in some toxic substance present in rice. Braddon (1907) in his monograph pointed out that the disease is endemic among rice-eaters but that those who live on certain varieties of rice escape. The prevalence and severity of the beri-beri depend upon the quantity of "active" rice consumed and the disease disappears when the particular local variety of rice is changed. He reasoned that the causal agent is a poison formed in stale or unsound rice by the action of a ferment, parasite, or epiphyte peculiar to "padi". The Japanese have postulated a specific "oryzatoxin" obtained from rice. The pioneer investigators of the action of rice polishings gave special names to substances obtained from the millings which have a prophylactic or curative effect, as they believed they were dealing with an antidote for a specific poison. Thus we have the "X-acid" (Hulshoff-Pol 1902) prepared from Phaseolus radiatus (the "katjang-

hidjoe" bean) also termed "aberic acid" (Tsuzuki et al. 1911). A flood of preparations were marketed as curative for experimental polyneuritis, e.g. oryzanin, torulin, orypan, antiberiberin, oridin, etc. Dissatisfaction with the vitamin hypothesis as being incomplete has again raised the question of rice toxicity. Megaw (1923), after careful study of beri-beri in Calcutta, agrees with the Japanese that human beri-beri differs from avian polyneuritis, and his findings led him to conclusions which virtually restate the theory of Braddon.

Following the classic experiments of Eijkman (1897) on avian polyneuritis, attention was increasingly diverted from rice toxin to the nutritive qualities of decorticated rice and to the preventive properties of rice polishings. The low phosphorus-content of polished rice and the high percentage in rice polishings led to the discovery that the lower the amount of phosphorus in a given diet the greater is the tendency to produce beri-beri, and a limit (0.4% P_2O_5) was fixed as the standard of safety for rice (Schaumann 1910, Fraser & Stanton 1909). The announcement by Funk (1911) of an antineuritic principle in rice polishings marked the foundation of the vitamin-deficiency theory which is now accepted by many as an established fact. McCarrison (1928) not satisfied that an avitaminosis explains all the facts, seeks to reconcile two opposing

theories by suggesting that the causus morbi is a toxic agent produced by disordered metabolism arising from a diet deficient in vitamin B. or B_1. (It will be noted how similar is Mellanby's (1931) compromise in connection with pellagra). The vitamin-deficiency theory has been based upon the identity, in whole or in part, of avian poly-neuritis with human beri-beri but this assumption is seriously challenged by several who have made an intensive study of the problem, notably by McCarrison (1918 et. seq.).

IX. GENERAL COMMENTARY

There can be no doubt that a diet restricted to or containing a preponderance of cereals is injurious to man and animals. An examination of the various experimental diets recorded in the section dealing with animal experiments (pp. 52-68) makes it evident that the common positive factor is a high cereal content. This is equally true of the synthetic diets used for the development of vitamin B deficiency disorders, which contain, on an average, 60-70% of rich starch. It is also an established clinical fact that a mixed diet, containing milk, eggs, meat, vegetables and fruit, definitely prevents or cures pellagra and beri-beri in man, and the related pathological conditions found in experimental animals.

Without prejudice to the part played by vitamins, it must be emphasised that one effect of a mixed diet is an appreciable reduction in the amount of cereal consumed, and, particularly in the case of animals, such a diet is invariably followed by increase of appetite with increased intake of food. That the palatability of the food plays an important part in the effect of an abnormal diet upon certain animals is often forgotten and sometimes denied, but in reality can be readily observed. In the case of monkeys and dogs whose senses of taste and smell are highly

developed, the animals turn from an unnatural and monotonous diet of cereal until forced by hunger to eat, and even then the appetite of need is soon satisfied. Whenever the experimental diet is made more inviting by admixture with some palatable constituent, the amount of food consumed is proportionately increased. In the interpretation of animal experiments, therefore, the part played by partial starvation must be allowed for or, if possible, avoided. On the other hand, the amount of cereal in the dietary is a factor in the rate of development of symptoms. It has been proved that the onset and severity of beri-beri in man and of polyneuritis in fowls is directly related to the quantity of rice consumed, and, in areas where it is endemic among maize-eating peoples, pellagra is similarly connected with the amount of maize in the diet of pellagrins. These facts strongly support the view that rice and maize possess definite pathogenic properties.

The reaction of different animals to staple cereal diets varies. Pigeons and fowls thrive on unhusked grain which, eaten in comparable proportion, produces profound disturbance in pigs, dogs, and monkeys. Man, the most highly susceptible of all to even moderate departures from a balanced diet, likewise shows great variation in his response to cereals. Only a proportion, for example, of the vast numbers who exist on rice ever develop beri-beri.

McCarrison has pointed out that in the Madras Presidency beri-beri is endemic in certain areas even among users of unpolished rice. Contrary to the accepted belief, the Hindus of these endemic localities, who are the greatest rice-eaters, suffer least of all, while the Pariahs, native Christians, and Mohammedans, who have a much more varied diet, are very susceptible to the disease. The rapidity with which Europeans contract beri-beri on rice diet suggests that native rice-eating peoples have a more highly developed tolerance.

Allowing for the metabolic peculiarities between the various species, it is apparent that the fully developed injurious effects of a restricted cereal diet upon man and animals are not essentially dissimilar. Clinically these are evidenced by malnutrition, cutaneous trophic disturbances, and symptoms of nervous disorder with sensory and motor involvement. The accompanying pathological changes, particularly in the nervous system, are closely related, their differences being mainly those of degree. It is more than mere coincidence that wheat diet in pigs, maize and rice in monkeys, and rye in dogs are followed by structural nervous changes of the same type as those found in human pellagra and beri-beri, two diseases of undoubted dietetic origin and, in the vast majority of cases, associated with a preponderance in the diet of cereals such as maize, rice,

and wheat.

The importance of the site and nature of the pathological lesions has been overlooked or under-estimated. I have pointed out that the visceral changes induced by a cereal diet are essentially those produced by an irritant poison and that the neurological picture is one of damage to the highly specialised nerve cells. From a knowledge of the trophic function of the neurone, especially in the vegetative or sympathetic system, it will be appreciated that, in addition to a malnutrition resulting from the ingestion of food of low biological value, we have a series of characteristic symptoms of dermatitis, muscular atrophy, and paralysis occurring in pellagra, beri-beri, and the related conditions following a staple cereal diet, which point to functional derangement of the nervous system, and which can be adequately explained by the nervous lesions demonstrated. It is also significant that the identical histological changes which follow the consumption over long periods of maize, and of other diets stated to be deficient in some essential accessory factor, can be faithfully reproduced in a short time by administering small amounts of a poisonous principle to monkeys maintained upon an unrestricted diet containing liberal amounts of the vitamin complexes.

To relate such identity of pathology with identity of

etiology seems logical. It is when the question of the etiological factor arises that the dangers of fallacy are encountered. It would appear simple and attractive to attribute the cause to the absence of some such factor as a vitamin, but at the outset it seems impossible to reconcile a positive intoxication with such a negativistic theory, unless it be admitted that the actual causus morbi is a positive toxic agent which ~~is~~ may be neutralised or, in some physiological complex way, inhibited by the presence of small amounts of one or more vitamins. Moreover there are certain definite observations which provide serious obstacles to the theory of mere absence of vitamins as the actual causal factor. In the U.S.A. Hygienic Laboratory Bulletin No. 116 (1920) Voegtlin, Neill and Hunter record a definite experiment carried out with pellagrins, in which they found that the administration of yeast and rice-polish extracts over a considerable period of time, and in large amounts, failed to modify the clinical course of the disease in well-marked attacks of pellagra. Such preparations were chosen for their high content in antineuritic vitamine as shown by their efficiency in the treatment and prevention of poly-neuritis in pigeons. Alcoholic extract of liver, however, was followed by a clinical improvement comparable to that produced by the consumption of liberal quantities of milk, eggs and meat. It would now appear that neither the yeast nor the liver extracts would contain much of the pellagra-

preventing factor (B_2) which is reputed to be insoluble in alcohol (92%), and yet their results were in striking contrast. It is also a surprising fact that maize contains as much (if not more) B_2 than rice or wheat, and yet the latter produce beri-beri and only rarely pellagra.

It is now established that neither is beri-beri confined to rice-eaters nor pellagra to those who live on maize. Beri-beri has occurred where wheat flour has bulked largely in the diet (Holst 1911) or has formed the staple food (Little 1912). Pellagra has been found where no maize was eaten. Numerous analyses of the diet of pellagrins by American authors show that other cereals such as wheat are pellagrogenic. 300 cases occurred in the British Mesopotamian Expeditionary Force while subsisting on a diet of white flour, biscuits, and tinned meat (Willcox). Rice has been conclusively associated with pellagra in Malaya (Sheppard 1912, Viswalingam 1918), Africa (Stannus 1913), China and Japan. The Tropical Diseases Bulletin shows that some 10 or 12 cases have been reported in detail in China since 1919, and according to Takahashi (et. al. 1929) over 70 cases have been recorded in Japan.

The accounts of Stannus and Viswalingam establish the fact that a diet commonly associated with beri-beri can cause typical pellagra. The relationship between these two diseases becomes more apparent when regarded from the point of view of their pathological basis. Both conditions are characterised by the same scattered diffuse myelin

degeneration of the peripheral and central nerve tracts, and by well recognised changes in the nerve cells of the peripheral ganglia and central nervous system. It is true that the degenerative changes in the cells of the brain so common in pellagra have not been demonstrated in human beri-beri, but the identical morphological appearances are found in the spinal cord in the latter as well as in the former. The polyneuritis of beri-beri is but the so-called "central neuritis" of pellagra located in the extra-cranial area of the nervous system. I have demonstrated from the experimental pathology that the lesions are the outcome of an intoxication primarily affecting the nerve cells.

The same observations may be applied to the disease known as "convulsive ergotism", commonly associated with ergotised rye. The investigations of Stockman and myself suggest that rye, like maize, can induce toxic symptoms in monkeys, with pathological lesions similar to those found in maize-fed animals. The records of epidemics of spasmodic ergotism (vide Barger 1931) present a clinical picture closely resembling pellagra. It is highly improbable that the ergot fungus, which no doubt is responsible for the gangrenous form, plays any essential part in the production of the convulsive type. The latter I believe to be due to the excessive consumption of actively poisonous varieties of rye.

The confusion attending the question of the etiology of pellagra and beri-beri has mainly arisen from (1) the idea that each is an isolated clinical entity, (2) the undue emphasis laid upon certain individual clinical features, and (3) the vitamin-deficiency conception of these diseases. The very name "pellagra" for example, has constantly focussed attention on the skin lesions, and some hold that experimental pellagra has never been produced in animals because the classical pellagrous rash found in man has never been faithfully reproduced. On the other hand, it has been too readily assumed that malnutrition with loss of hair and scaliness of the skin in rats is experimental pellagra. I would suggest that the marvellous symmetry and the nature of the dermatitis are more properly referable to the underlying nervous degeneration, and form only one of the clinical evidences of a trophoneurosis which is not peculiar to pellagra.

The rôle played by vitamin deficiency calls for comment. The evidence for the existence of vitamins seems clear, especially in the light of progress in connection with the antiscorbutic and antirachitic factors. It is nevertheless significant that the current conception of pellagra and beri-beri as being solely due to the lack of particular vitamins is being seriously questioned. The present

studies serve to intensify the dissatisfaction with the vitamin-deficiency hypothesis. The feeding of certain cereals to animals along with a supply of vitamins A, B, C, and D, has been shown to produce symptoms and pathological changes of the same nature as those found in pellagra. From maize, as well as from other cereals, an active poison has been isolated which can reproduce in monkeys, with astonishing rapidity and accuracy, a pathological syndrome found in human pellagra and in animals fed on diets deficient in vitamins A and B. One is forced to the conclusion that those "deficiency" diseases typified by beri-beri and pellagra are produced by the direct action of certain acidic poisons which, in the case of a mixed diet, are not present in sufficient amount to be pathogenic. The vitamins may prove to be direct antagonists of these poisons or, more probably, to provide for their neutralisation by virtue of hormone-like qualities.

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