Winter and Smith. The insulin prepared from these sources appears to differ from that prepared from pancreas, in that its action in lowering the blood sugar is delayed, sometimes for a day or so, which is also the case with an insulin-like substance prepared by Collip from various vegetable sources, and styled by him, in recognition of these differences, "glucokinin." Best and Scott have also succeeded in preparing insulin, or insulin-like substances, from various other sources. It would appear, therefore, that the distribution of hormones capable of accelerating the disappearance of glucose from the blood is widespread, not only in the animal kingdom but in the vegetable as well; it is probable, however, that these do not all have the same physiological action. In the investigation of this we must bear in mind that many substances have been known for long to be capable of lowering the blood sugar—for example, peptone, hydrazin, certain mineral salts, phloridzin, etc. All of these also cause glycogen to disappear from the liver, and indeed certain of them cause structural changes in this organ. Although it would certainly be desirable to have substances like glucokinin having a more prolonged action than insulin in depressing the blood sugar, we must exercise some caution in recommending them for clinical use until it is certain that they have no deleterious effects on the liver. It is possible also that these substances merely stimulate the secretion of insulin from the pancreas of the animal into which they are injected, or serve as precursors for its production. If such be the case, then they can have little value in diabetes.

I have endeavoured in this review to adhere strictly to ascertained facts, and have refrained from venturing to speculate with regard to the numerous problems in metabolism, both of animals and plants, for the investigation of which insulin may prove a useful instrument. If I have succeeded in giving a bird's-eye view, as it were, of the results that have been obtained, I shall consider that my efforts have not been in vain, and I shall feel repaid if, as an outcome, others join us in the work on insulin.

REFERENCE.

¹ G. S. Eadie: BRITISH MEDICAL JOURNAL, July 14th, 1923, p. 60.

THE RELATION OF FAULTY NUTRITION TO THE DEVELOPMENT OF THE EPITHELIOMA CONTAGIOSUM OF FOWLS.

(With Special Plate.)

BY

ROBERT McCARRISON, M.D., D.Sc., F.R.C.P.,

LIEUT.-COLONEL, INDIAN MEDICAL SERVICE,

IN CHARGE OF THE DEFICIENCY DISEASES INQUIRY, INDIAN RESEARCH FUND ASSOCIATION; PASTEUR INSTITUTE, COONOR.

EPITHELIOMA CONTAGIOSUM (avian variola; fowl-pox; chicken-pox; epitheliosis; pigeon-pox; canker) is a disease of birds which has been described as follows:

It is characterized by "the appearance of wart-like nodules, varying in size to that of a pea, or slightly larger, on those parts of the skin of the head where feathers are few or absent, such as the nostrils, openings of the ears, the comb, wattles, and the eyelids, the last named being one of the most common sites. The nodules are encapsuled, firm in consistence, with a caseous centre, and usually remain discrete, but a number situated closely together form a mulberry-like mass. In some cases the contents resemble fatty tissue, except for being more vascular; in others they are warty and contain flakes of coagulated material very much like small clots of milk. Lesions are also found on the buccal mucous membrane, the affected parts of which become covered with thick whitish-yellow exudate, in appearance resembling that of ciphtheritic false membrane."¹

"Marx and Sticker, in 1902, demonstrated that the disease was due to a virus which was capable of passing through a Berkefeld filter, and their results were confirmed by Juliusberg and Hertzog. Burnet, however, obtained very varying results in his filtration experiments. He found that the virus was frequently arrested by the Berkefeld filter, although the infective material had been largely diluted with water. It has not been possible to cultivate the virus artificially, and its nature remains a matter for further investigation. It exists in the blood, internal organs, and in the fluids expressed from the lesions, and is possessed of considerable

resistance to the action of heat* and antiseptics. The disease can be transmitted by rubbing juice from the lesions into an area of skin from which the feathers have been removed, or which has been lightly scarified, and the lesions then produced are confined to the part inoculated. According to Burnet, it can also be transmitted by intravenous inoculation and by feeding, and the lesions develop at the predilection seats of the disease."¹

"The microscopic examination of the epithelioma of the skin shows, according to Polowinkin, the epithelial layers thickened and the epithelial papillae elongated inward; in the papillary layer the vessels are dilated and, like those of the subcutis, surrounded by migrating leucocytes; in addition there are small haemorrhages into the tissue of the papillary layer. Cell-inclusions are found in the swollen epithelium, similar to Guarnieri's pox-bodies (Loewenthal, Burnet). In a general way the characteristic features of the efflorescences are composed of a more or less pronounced hyperplasia and proliferation of the cell elements of the skin, which sooner or later succumb to degeneration. This is associated with the extension of the process to the external skin and there follows a condition which, according to Reischauer, is similar to true pox; the difference lies mainly in the fact that in bird-pox the more chronic character of the disease causes the nodular and tumour formation to predominate."²

My purpose here is to record the occurrence of epithelioma contagiosum in pigeons under conditions which indicate that nutritional factors may play an important part in its development. The observations have another and a more general interest, inasmuch as they tend to show that a certain state of faulty nutrition, and of deranged metabolism, favours the entry into the body and the activity of an invisible virus possessing the specific property of inducing epithelial new growth.

Experiment.

Polyneuritis columbarum was produced in a number of pigeons by exclusive feeding on washed milled rice. Twelve of them were "cured" at the height of the disease by artificial feeding with green *mung dal*. Within forty-eight hours of the disappearance of polyneuritic symptoms they were placed in an open-air pen with sixty healthy stock birds, and had access to the mixture of grains found to be most suitable, in this climate and at this altitude, as a stock food for pigeons. It consists of one part of green *mung dal*, one part of *ragi*, and four parts of *cholum*. Thus, the birds, after the cure of the polyneuritis, received a food containing a sufficiency of vitamins and other essentials for their maintenance in perfect health. Owing to their poorer nutrition when put into the stock-pen, they were less able to protect themselves against attack by their more lusty companions. The lessened ability to escape injury and to recover from it is an important effect of faulty food on the animal organism, and in this instance abrasions about the head—the most frequent seat of injury—appear to have favoured the entry of the virus of epithelioma contagiosum. In general, then, the twelve "cured" birds were more subject to injury than their fellows. Nevertheless, as weeks passed they appeared to prosper; their plumage improved and their body weight rose. Six weeks to three months after they were put into the stock-pen seven out of the twelve developed epithelioma contagiosum (Fig. 1), while their sixty healthy well fed companions remained free from it.

The growths occurred about the angles of the mouth, on the eyelid, the nostril, in the neighbourhood of the ear, and in the floor of the mouth beneath the buccal mucous membrane (Fig. 1). Their histological characters are shown in the photomicrographs (Figs. 3 to 6). The epithelial downgrowths stimulated in appearance those seen in such a condition as carcinoma of the penis in man. The epithelial new growth was infiltrative to a limited extent, had local destructive properties, and its cells tended to undergo rapid degeneration.

The nodules were emulsified, and the emulsion was rubbed into lightly scarified surfaces at the angle of the mouth of six healthy and well-fed pigeons. In two of these diphtheritic false membranes developed, and one of them died from the extension of the false membrane backwards, resulting in interference with swallowing and in involvement of the air passages; the second recovered. The other four were unaffected. In none did the inoculation of the emulsified nodules cause infiltrative new growth of epithelium. It would seem, therefore, that these well nourished birds were resistant to the influence of the growth-inducing virus, since those affected by its inoculation exhibited only superficial lesions. It appears likely that the virulence of the virus was not great; it was great enough to cause typical lesions in birds whose nutrition was faulty, but not so great as to be capable of causing infiltrative lesions in healthy, well-nourished birds.

*In this respect resembling the growth-promoting substance evolved during the process of autolysis of tissue cells.²

FIG. 1.—Epithelioma contagiosum in pigeon (right-hand figure); normal control bird (left-hand figure). Section of epithelioma from this case is shown in Fig. 3.

FIG. 2.—Epithelioma contagiosum involving the floor of the mouth.

FIG. 3.—Section of nodule showing infiltrative new growth of epithelium; early stage before degeneration of cells has begun.

FIG. 4.—Advancing edge of growth invading floor of mouth, showing epithelial downgrowths and swollen epithelium containing cell inclusions.

FIG. 5.—Low-power photomicrograph of epithelial growth advancing from buccal mucous membrane into the tissues forming the floor of the mouth.

FIG. 6.—Section of nodule from the nostril. Low-power magnification showing the characteristic epithelial downgrowths and islets of epithelium: a number of the latter show degenerative change in their centres.

The development of epithelioma contagiosum in seven out of twelve birds which had been subjected to previous vitamin depletion, at a time when sixty others not so depleted escaped the malady, indicates that this depletion combined with other food faults was responsible for the occurrence of the disease. Before they were put into the stock-pen the birds had been fed on washed milled rice to a point at which typical polyneuritis columbarum developed. Now while the polyneuritic symptoms are directly attributable to the absence of vitamin B from this dietary, the disorder of metabolism and the changes in the body tissues are the consequence not only of this want but of the excess of starch and the deficiency of protein, fats, and inorganic salts associated with it.⁴

Outside the laboratory pure and complete avitaminosis must be extremely rare, but partial avitaminosis is common in human dietaries, and is always, or almost always, associated with other deficiencies or excesses or both. Indeed, the permutations and combinations of food deficiencies with food excesses are numerous, and in practice it may be expected that the disturbances of metabolism, and the symptoms resulting from them, will vary according to the particular combination of food faults in the diet.

The belief is now common that vitamin deficiency, so far from favouring tumour growth, is actually unfavourable to it. But in appraising the significance of any such effect of vitamin deficiency not only must the degree of avitaminosis be considered, but also the other food faults by which it is accompanied. If the avitaminosis be complete, growth of any tissue will become impossible; whereas if it be incomplete it may favour the operation of a growth-inducing factor. While, therefore, complete avitaminosis, or extreme degrees of it, protracted over long periods, may be unfavourable to the growth of tumours in laboratory animals, the case may be different in practice, where avitaminosis is rarely, if ever, complete, but is often of sufficient degree to play an important part in association with other food faults in bringing about disordered states of metabolism not necessarily incompatible with life, but incompatible with perfect health.

The condition of the "cured" birds at the time of their entry into the stock-pen had been produced rapidly, but it results as surely, although more slowly, when the vitamin deficiency is less drastic. In a high percentage of the birds the function of the gastro-intestinal tract was greatly impaired.⁴ The restoration of this function takes time and is not coincident with the cure of the polyneuritic symptoms. In all the birds the liver had lost approximately one-third of its total cells, and approximately one-third of its total content of nucleic acid. In all the gonads were atrophic, involving a deficient supply to the body of their internal secretions. The function of the adrenal glands, which is intimately related to the metabolic processes of the animal organism, was deranged in all⁴; and although in a proportion of polyneuritic birds the provision of suitable vitamins restored in part this function, yet restoration had not occurred in the birds affected by the virus of epithelioma contagiosum. Further, the vitamin depletion involved a loss of body lipoids and changes in the reaction of the body fluids and tissues. Though the polyneuritic symptoms are the most obvious evidence of vitamin depletion, they are not the most important; for while they usually disappear rapidly with the provision of the missing vitamins, recovery from the less obvious metabolic disturbances and pathological changes is slower. After the cure of the polyneuritic symptoms the birds had access, for periods of from six weeks to three months, to a food mixture that sufficed for the maintenance of perfect health in previously healthy birds; but although they appeared to eat well of the food provided, yet it did not suffice, within the period, for the complete restoration to health of birds previously depleted of vitamins; it did not protect them against the action of the virus which causes infiltrative new growth of epithelium. Nor did it suffice, as appeared on *post-mortem* examination, to restore the deranged function of endocrine organs. In birds which developed epithelioma contagiosum it was found that the adrenal enlargement consequent on avitaminosis had persisted and had indeed in most cases become exaggerated.

The combined weight of both glands ranged between 40 and 110 mg.; in two cases it reached 100 and 110 mg. respectively. Their average weight was 75 mg., or 375 mg. per kilogram of body weight; the normal figures being 26 and 95 mg. respectively. In one male the testicles weighed only 10 mg.; in another 30 mg., and in a third 320 mg.; the normal average weight is 1,355 mg.

The adrenal hypertrophy and the atrophy of the gonads was evidence that the disordered state of metabolism, induced by previous vitamin depletion, had not been recovered from. It seems likely, indeed, that the derangement of endocrine function induced by avitaminosis was a factor of importance in the development of epithelioma contagiosum in these cases.

Looking at the matter from the point of view of the combination of factors concerned in the development of the epithelial new growths in this particular instance, we find this combination to have been:

1. Lessened bodily vigour; which favoured the occurrence of injury or abrasion of exposed parts, and the entry into the body of a growth-inducing virus.
2. The fortuitous presence in the pigeon-pen of an invisible virus possessing the property of inducing infiltrative new growth of epithelium.
3. An abnormal state of metabolism, with disorder of endocrine function, favourable both to the entry of this virus into the body and to its activity therein.

Apart from the fact that deranged metabolism, induced by faulty food, appears to favour the development of epithelioma contagiosum in birds, this combination of causal factors deserves consideration from a more general point of view. Given the intervention of a factor possessing growth-inducing properties it is possible to suppose that faulty food may induce in the animal organism such a state of deranged metabolism that this factor may become operative and epithelioma may arise. In the experiment here recorded the epithelial growths were more or less benign, but the significant fact is that the combination of causes which existed favoured the development of epithelial new growth.

It is not suggested that all these conditions must invariably be satisfied before epithelioma contagiosum can arise; it is possible that the virulence of the virus may vary, and may sometimes be so great as to cause epithelial growths even in birds whose nutrition is perfect. Since disordered states of metabolism consequent on vitamin depletion and the food faults associated with it are favourable to the operation of this invisible virus, they are probably also favourable to the operation of others possessing like properties. The virus in the experiment here recorded must have been introduced into the body, and it is possible that in nature there are others possessing the property of inducing new growth whether of epithelium or of other tissue cells. In this connexion I am reminded of the association of carcinoma and of sarcoma in rats with infection by certain nematode and cestode worms—such, for instance, as *Spiroptera neoplastica* (Fibiger) with carcinoma of the stomach; and *Taenia crassicolis* (Rohdenburg and Bullock) with sarcoma of the liver. It is conceivable that these parasites produce poisons possessing inherent growth-inducing properties. If this were so vitamin depletion might well be a "limiting factor"* as important in the development of these growths in rats as it is in the development of epithelioma contagiosum in pigeons.

It is indeed conceivable that substances possessing this property may be evolved from the tissue cells themselves under conditions of slow disturbance of nutrition, in a manner comparable to the evolution of such during the process of autolysis of cells.² Many of the effects of avitaminosis resemble, as shown by Cramer and his co-workers, those produced by exposure to x rays; the development of epithelioma in man or of sarcoma in rats following injury by x rays may be related to disturbance of the nutrition of cells induced by these rays. If it could be shown that a growth-promoting factor is evolved in tissues

* This term is used in its agricultural sense, a lacking condition, the insufficiency of which prevents proper growth.

over-exposed to x rays, then x-ray burns would provide a combination of factors favourable to the development of epithelioma analogous to that which caused the development of epithelioma contagiosum in pigeons—injury, disturbed nutrition of cells, and the possible presence of a conjecturable growth-promoting factor.

Having regard to the profound degenerative changes which are produced in the gastro-intestinal tract by faulty food deficient in vitamins,⁴ and to the ease with which, in these circumstances, harmful substances may find their way into it, or may be formed in its contents, it is possible to suppose that among these substances there may, at times, be some possessing growth-inducing properties. In this connexion attention may be drawn to the occurrence of a carcinoma of the pylorus in an early stage in one of my monkeys fed on a diet of autoclaved food, butter, and onion.⁴ Although I cannot affirm that this carcinoma had actually developed within the period of the experiment, yet the observation is to be borne in mind in connexion with the considerations raised in this paper.

REFERENCES.

- ¹Hoare, E. W.: *A System of Veterinary Medicine*, 1913, vol. i, p. 323.
²Drew, A. H.: *Lancet*, April 28th, 1923, p. 834. ³Hatyra and Marek: *Special Pathology and Therapeutics of the Diseases of Domestic Animals*, 1912. ⁴McCarrison, R.: *Studies in Deficiency Disease*, 1921.

RADIOGRAPHIC LOCALIZATION OF SPINAL LESIONS BY SICARD'S METHOD.*

(With Special Plate.)

BY

PERCY SARGENT, C.M.G., D.S.O., F.R.C.S.,

SURGEON TO ST. THOMAS'S HOSPITAL, AND TO THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC.

DURING a recent visit to Paris Professor Sicard kindly demonstrated to me his method of localizing certain spinal lesions by radiography after injecting an opaque fluid into the spinal theca. It provides us with a new means of diagnosis of great value.

Briefly, Professor Sicard's method is as follows. A small quantity, between 1 and 2 c.cm., of lipiodol is injected into the spinal theca through a suboccipital puncture, the patient being in a sitting posture. Lipiodol is a heavy oily fluid consisting of "huile d'oeillette" containing 40 per cent. of iodine, and is remarkably opaque to the x rays. The lipiodol sinks slowly downwards and is arrested at any point of occlusion of the spinal theca, so that the upper limit of a tumour, for instance, can be accurately demonstrated by x-ray examination. Similarly the lower limit of such a tumour can be shown by injecting the lipiodol through a lumbar puncture, and taking a radiogram with the patient in the head-down position. The three cases in which I have employed this method are as follows:

CASE I (Under the care of Dr. M. A. Cassidy).

An intrathecal neurofibroma compressing the cord at the level of the ninth thoracic segment. The curved lower border of the shadow defines clearly the rounded upper surface of the tumour (Fig. 1). The two small shadows situated lateral to the main mass mark the position of a posterior root ganglion. The tumour was removed, and the patient made a rapid and uninterrupted recovery.

CASE II (Under the care of Drs. H. G. Turney and A. E. Russell).

An extrathecal endothelioma at the level of the eighth thoracic segment. The radiogram (Fig. 2) showed the lipiodol to have been completely arrested at the level of the body of the sixth thoracic vertebra. In this case the neurological signs were such as to render it doubtful whether the case was one of spinal compression at all, whilst at the same time the exact segmental level was difficult to define. The radiographic examination immediately and almost dramatically settled both these questions. Laminectomy was performed and the tumour was removed.

*A paper communicated to the Section of Surgery at the Annual Meeting of the British Medical Association held at Portsmouth.

CASE III.

Fracture-dislocation at the level of the first lumbar vertebra. Here the radiogram (Fig. 3) shows the narrowing of the spinal canal and the upper limit of thecal occlusion. It also shows small droplets of lipiodol arrested at various points, probably demonstrating the presence of arachnoidal adhesions.

Even from these few cases the value of Sicard's method is obvious. Not only can it be employed to ascertain whether or not a block exists in the spinal theca, but it shows the exact position of the lesion with relation to the bones. From the operative standpoint the localization is more accurate than that which can be arrived at by neurological examination. Neurological signs may enable the segmental level to be accurately determined, but the exact position of any given spinal segment with relation to the bones is by no means easy to ascertain. Consequently a radiographic demonstration of the relation of the lesion to the vertebrae is of great value, and enables a tumour to be exposed by the removal of perhaps only three laminae arches. If, the upper limit of a tumour having been defined, a second examination is made by taking a radiogram with the patient placed head downwards after injecting lipiodol through a lumbar puncture, the lower limit of the tumour can also be demonstrated. This is a point which cannot be ascertained by neurological examination, but it is a matter of considerable importance to the surgeon, since tumours extending over many segments are sometimes encountered.

I am indebted to Sir Archibald Reid and Dr. Fildes for the excellent radiograms from the radiological department of St. Thomas's Hospital.

Memoranda :

MEDICAL, SURGICAL, OBSTETRICAL.

A LONG PAROXYSM OF AURICULAR FIBRILLATION.

Mrs. M., now aged 74, was seized on November 15th, 1919, with right hemiplegia and aphasia. The pulse was hard, regular, and slow. Early on November 17th she became faint with cold clammy skin, and later in the day it was found that auricular fibrillation had set in, the pulse rate averaging 130. On November 24th this attack ceased, and the pulse was regular at 64. On December 3rd fibrillation once more appeared, and its onset was apparently associated with the same symptoms of heart failure as before. From this time onward till July, 1921, a period of eighteen months, she was seen at first weekly and later about once a month, and during the whole of this period the pulse remained quick, and wholly irregular. At my July visit the pulse was found to be regular at 60 a minute. Since that date she has had three paroxysms of fibrillation, each of a few days' duration, and each time she has become collapsed and somnolent at the onset of the attack. When the heart is regular, the rate is slow (50 to 60), and the symptoms of heart failure at the commencement of fibrillation are doubtless dependent on the great increase of rate. As she is constantly in bed she apparently becomes inured after a time to the defective circulation. The polygraph curve during an attack shows a wholly irregular pulse without accurate spacing of the beats, such as is found in the irregular pulse of auricular flutter.

It is well known that a paroxysm of auricular fibrillation may continue for some months and then cease (Mackenzie), but it is probably very unusual for an attack to last as long as a year and a half. It seems fair to assume that during the whole of this period fibrillation was present even though the patient was seen only once a month during the latter part of the period. The onset of tachycardia is always associated with the prominent symptoms of heart failure, and these would almost certainly have been observed and reported to me by her daughter had there been any return of the normal rhythm followed by a fresh paroxysm.

Hull.

E. E. LASLETT, M.D.