CONCLUSION

It will be realized that the study of the defence mechanisms of the body has not at present passed very far beyond the descriptive stage. Complete explanation and elucidation are not yet in sight. The haemolytic complement of serum is possibly the simplest of all the factors so far described, and consequently offers the greatest hope of ultimate explanation. Even in this case, however, the usual view that complement is a particular physical state of the serum proteins is not universally accepted as proved, nor can it be until a clearer picture is available of the molecular structure of proteins in solution and the way in which this structure is affected by temperature, reaction, etc. The amphoteric character of proteins—or, in other words, their more or less feeble powers of combining with either acids or bases, or with each other—is without doubt responsible for their power of building up into aggregates of relatively enormous size, but the forces which hold these aggregates together are often so feeble that protein systems in solution are extraordinarily labile and sensitive to relatively mild agencies. On this account a quantitative physical chemistry of proteins is only as yet beginning to emerge, and considerable time must elapse before a theory of complement structure on the lines hinted at above can be either prudently formulated or adequately tested.

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SOME EARLY OCULAR SYMPTOMS OF
OVER-INDULGENCE IN SUGAR AND
SWEET FARINACEOUS FOOD

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In a series of interesting papers published recently in the *Edinburgh Medical Journal*, Dr. J. Hunter Paton¹ has drawn attention to the great increase in "the national consumption of sugar within recent years in its relation to the occurrence of disease." Glucose is the end-product in the biochemistry of the carbohydrate constituents of the dietary, and it is well known that the capacity to digest and assimilate sugar and starch varies greatly in different individuals. Those whose powers are more than usually restricted in regard to such foods readily suffer from diseases especially associated with disorders of carbohydrate metabolism.

The functional activity of every organ of the body is regulated by the quantity and quality of the blood circulating in its capillaries. Krogh² has demonstrated that the part played by the capillaries is distinct from that of the arteries and of the veins. They are not simply tubes through which blood flows. The cells of the organ have a direct influence upon them. They open up, or close down, in response to the call of the tissues for nourishment, and in the marvellous biological adaptation of structure to function the capillaries play an important part. Much depends upon their size and on the permeability of their walls to colloids.

DISTURBANCES OF VISION AND THE DIET

Visual function depends upon the circulation of the blood in the capillaries of the retina and the choriocapillaris. In proportion to its size the eye is very abundantly supplied with capillaries. Those of the retina and the choriocapillaris are among the most delicate in the body; and in the eye, as elsewhere, "all the secret and intimate business of life is transacted through their walls" (Allbutt). In the structures peculiar to the eye, however, perfect transparency is the primary requisite, and Nature has made provision for this by the relative impermeability of the walls of the ocular capillaries to the passage of colloids (Duke-Elder). The peculiar translucency and the characteristic colour of the normal fundus oculi³ are both due to circulation of the blood in these relatively impermeable capillaries. Dale⁴ has demonstrated that dilatation of the capillaries and increased permeability of their walls to the passage of colloids are brought about very rapidly by the action of metabolic toxins. One of the earliest clinical signs of this form of toxæmia is a diminution in the translucency of the ophthalmoscopic picture—a condition analogous to a muddy complexion. Although this appearance is difficult to describe, it is easy to recognize after attention has been directed to it. Translucency is the most delicate quality of the normal fundus oculi, and any loss of this pristine brilliancy is the first sign of a departure from health.

Among the patients suffering from headache referred to an ophthalmic surgeon is a well-defined group which does not obtain the relief expected from the use of the glasses prescribed.⁵ In these patients the ophthalmoscopic examination of the fundus reveals subtle changes in colour and translucency, which are probably due to interference with the rate of the circulation of the blood in the capillaries of the retina, and to increased permeability of their walls to colloids. The light sense is always more or less disturbed. Patients complain either that they require more light than formerly or that the light must

be reduced in intensity to enable them to see with comfort; and some tell of difficulties they have when working with certain colours. The headache, although aggravated by the use of the eyes, is almost invariably present in the morning on first waking from sleep, and further evidence of metabolic disturbance is revealed by an examination of the urine. A specimen kept overnight in a urine glass is usually found to contain large numbers of minute crystals of oxalate of lime when the deposit is examined under the microscope. The patients are often said to suffer from "goutiness"; but they improve much more rapidly when the intake of sugar and carbohydrates is restricted than when the nitrogenous forms of food are cut down. As a result of suitable general treatment, in addition to the use of accurately adjusted spectacles, the capillary congestion of the retina diminishes, the fundus oculi regains its normal translucency, the visual symptoms disappear, and headache is permanently relieved.

PHLYCTENULAR CONJUNCTIVITIS

Let me give one more example. Nutritional disturbances, similar in their nature to those I have described, are the primary cause of phlyctenular conjunctivitis. This disease is invariably the result of over-indulgence in sugars and sweet starchy foodstuffs. The first attack always occurs in early childhood. It is probable, therefore, that the patients all suffer from what Garrod⁶ calls "an inborn error of metabolism." Both eyes are usually more or less affected, and in many instances the ocular condition is so acute and so urgent that attention is diverted from the constitutional factor. There is probably something wrong with the general make-up of the child; but the exciting cause of an attack can always be traced to an excessive consumption of carbohydrate foods, and more particularly to a surfeit of sugar. In the majority of cases this unsuitable dietary is aggravated by want of fresh air and by an insanitary environment. The ocular signs are always part of a larger process. The child suffers from impaired digestion and defective assimilation for a considerable time before the eye symptoms develop. He has a pasty, muddy complexion—pallor veiled by lividity—and is often fat and unhealthy-looking as a result of an increased water content of his tissues (Cameron).⁷ The tongue is coated, and the papillae on its surface are abnormally prominent. The teeth decay very early, and the carious condition of the milk teeth is followed by a similar condition of the second dentition. The bowels are easily upset, constipation alternates with diarrhoea, and the motions are often foul-smelling, and of unnatural colour and consistency. The urine is scanty, deposits urates, and frequently contains traces of indican and sugar.

Photophobia is one of the earliest and most characteristic symptoms. It is most distressing. The slightest exposure of the eyes to light causes acute pain; but if the child be allowed to remain in a dark corner of a room he usually opens his eyes and amuses himself with his playthings. In health we are not conscious of the direct light reflex; but in phlyctenular conjunctivitis the circular muscle of the pupil contracts spasmodically. Spasm of the circular fibres of the iris is the cause of the photophobia, which will persist until the spasm is relieved. Whenever the muscle is paralysed by atropine the photophobia disappears. In these circumstances, however, the action of the drug is of much shorter duration than normal, and the intolerance of light recurs as soon as the mydriasis begins to pass off. The mechanism of the production of photophobia is therefore spasm of unstriated muscle. The contraction of the sphincter of the pupil brings the iris from a physiological point of view into line with the hollow viscera, in all of which pain is felt very acutely during spasmodic contraction of the unstriated muscle in their walls. Pain of this character has received

different names according to its location—photophobia in the eye, angina pectoris in the chest, strangury in the bladder, and colic in the abdomen. In every case, notwithstanding the difference in nomenclature, the pathological process is the same—namely, spasmodic contraction of unstriated muscle—and the pain disappears as soon as the spasm is overcome. Photophobia, unaccompanied by any lesion of the cornea, is likely to be of constitutional rather than of local origin; and in phlyctenular conjunctivitis the cause of the trouble is disordered carbohydrate metabolism.

Photophobia is usually accompanied by localized congestions of the conjunctival blood vessels in the midst of which is a small phlycten or pustule. Photophobia is the most characteristic subjective feature of the disease, and the phlycten is the most characteristic objective feature. It is formed by a localized collection of lymph corpuscles, similar to the lymphoid tissue found in other parts of the body. The discrete character and the nodular manifestation of the inflammation are evidence of the existence of a constitutional cause, and that point of view is confirmed by the fact that the majority of the patients suffer also from hypertrophied tonsils, adenoid vegetations, and enlarged cervical glands.

Treatment

In the treatment of the disease it must be borne in mind that it depends upon a constitutional cause—chronic nutritional disorder, due largely, if not entirely, to derangement of carbohydrate metabolism. It is necessary, therefore, to give very particular directions regarding diet, and to insist that these directions be obeyed implicitly. At the outset sugar in every shape and form, pastry, potatoes, and all forms of sweet and starchy foods must be temporarily excluded from the dietary. Visible improvement follows quickly after the prescription of a diet with a relatively high protein content. As soon as the tongue begins to clean the intolerance of light lessens, the child opens his eyes, and takes an interest in his surroundings. Any indiscretion in diet, however, will at once determine a relapse. The child's intense craving for sweets, biscuits, and breadstuffs ought never to be forgotten. He will get them surreptitiously if he can. If he is not making satisfactory progress, it is almost certain that the prescribed dietary is not being faithfully followed. When sugar is present in the urine, it means nothing more than that the patient has had a surfeit of sugar and carbohydrates. The child's capacity to assimilate carbohydrates is not necessarily seriously impaired; but far too large a quantity has been consumed within a short space of time. Provided the intake is properly regulated, the processes of metabolism and excretion will be sufficient to deal with any excess; but difficulties will arise at once if the same quantity of glucose be consumed at a single sitting and more especially, as so frequently happens, when sweets are eaten habitually between meals. Insulin has no effect upon the symptoms. Tolerance for glucose must be regarded, therefore, as a "velocity," not as a "mass," and complete recovery will only take place after the dietary has been properly regulated. Proneness to relapse is part of the ordinary clinical picture of phlyctenular conjunctivitis; but recurrent attacks of a serious nature only occur in those patients who neglect the instructions given them regarding diet. If they adhere faithfully to the dietary prescribed for them they will continue to keep well, in spite of the unsatisfactory conditions they have to contend against in their own homes.

Concomitant Diseases

All the complications and sequelae of phlyctenular conjunctivitis are due to secondary infection. The patient's resisting power has been greatly enfeebled as a result of

improper dieting, and a "soil" favourable to the growth of all forms of micro-organisms has been cultivated. Bacteria which are always present and are usually quite harmless become active in these patients, giving rise to conjunctivitis and to ulceration of the cornea. In patients in whom the disease has existed for many weeks, therefore, ulceration of the cornea and all other dangerous symptoms are the result of secondary infection. The eyelids, nose, and the upper lip become swollen, and the skin of the face is covered by an eczematous eruption. Painful fissures form at the external canthus, the side of the nostrils, and round about the mouth. In addition, seborrhoea of the scalp, enlarged cervical glands, nasal and bronchial catarrh, and intestinal disturbances are common. It is all-important to remember that micro-organisms—that is to say "seed"—will only grow upon a suitable "soil." The general make-up of children who suffer from phlyctenular conjunctivitis is such that they offer feeble resistance to every form of infection, consequently they fall a ready prey to the ubiquitous tubercle bacillus. The clinical picture is always that of bovine tuberculosis, and it is very probable that in these patients who are attacked disordered carbohydrate metabolism has paved the way for the onset of the tuberculous infection.

It is probable that in many adults who suffer from toxic amblyopia—the result of over-indulgence in tobacco or alcohol or both—there is disturbance of carbohydrate metabolism, and that a systematic estimation of the blood sugar may prove an important factor both in prognosis and in treatment. A full investigation of this subject offers a promising field for research.

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THE GLUCOSE TOLERANCE IN RHEUMATOID ARTHRITIS *

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It was first demonstrated by Pemberton¹ that in true rheumatoid arthritis there was marked alteration in the metabolism of glucose. He showed that after administration of a standard dose of glucose the blood sugar rose rapidly to well above normal limits and subsequently fell sharply to the base line. The curves thus obtained somewhat resemble those obtained in exophthalmic goitre. The present investigation was undertaken partly to confirm these facts, but mainly (at the suggestion of Dr. R. D. Lawrence) to ascertain whether the normal difference between the sugar content of arterial and venous blood was altered. If this were found to be diminished it would suggest that the cause of the rapid rise of the blood sugar in these cases might be due to a failure of the muscles and other tissues to utilize the sugar, with consequent failure of their nutrition.

* A paper read before the Section of Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

TECHNICAL METHODS

For the estimations the micro-method of Folin-Wu was utilized throughout, at each stage 0.2 c.cm. of blood being taken from the median basilic vein and from the finger-tip of the patient. Blood obtained in this way from the finger-tip may be regarded as being practically arterial in character.

As the patients were all adult and practically all young women, it was decided to adopt a dosage of 50 grams of glucose as a standard; specimens were taken before administration and subsequently at intervals of three-quarters of an hour up to two and a quarter hours. In a few cases samples of urine were taken at the same intervals, whilst in a few others a specimen was collected at the end of the investigation only. The main fact that emerged from the urinary investigation was that the renal threshold for glucose is often abnormally high in rheumatoid arthritis. Some fifty cases were investigated in this manner, a few of these being controls or patients suffering from types of rheumatism not resembling rheumatoid arthritis, two being, in addition, true diabetics.

RESULTS OF INVESTIGATION

The following is a typical result obtained from a normal healthy person.

TABLE I.—Blood Sugar Percentage

	Before Glucose	$\frac{3}{4}$ Hour After	1½ Hours After	2¼ Hours After
Artery	0.081	0.145	0.136	0.115
Vein	0.077	0.136	0.120	0.109
Difference...	+0.004	+0.009	+0.016	+0.006
Urine sugar ...	Absent	Absent	Absent	Absent

It will be noted that the arterial blood sugar content is throughout higher than the venous, the difference being least before the administration of glucose and greatest one and a half hours afterwards. In a few control cases greater differences (that is, in the vicinity of 0.025 per cent.) were observed. In some instances it was found that the peak of the arterial curve came earlier than that of the venous curve, with the result that in the one-and-a-half-hour specimens of blood there was often a much higher value in the venous blood than in the arterial. This phenomenon was observed in some of the rheumatoid cases as well as in the controls.

The following result was obtained from a patient, aged 30, with true rheumatoid arthritis.

TABLE II.—Blood Sugar Percentage

	Before Glucose	$\frac{3}{4}$ Hour After	1½ Hours After	2¼ Hours After
Arterial	0.133	0.316	0.273	0.180
Venous	0.111	0.288	0.306	0.167
Difference...	+0.022	+0.028	-0.033	+0.013
Urine sugar ...	Absent	A trace	2.5 per cent.	A trace

This table illustrates well the very high peak values obtained, occurring in the arterial blood at three-quarters of an hour and in the venous at one and a half hours and followed by a rapid fall. This failure of the peaks to coincide produces a negative difference of 0.033 per cent. at one and a half hours, but it is already evident that the expected small differences between the arterial and venous values are not forthcoming. Though such small differences were observed in one or two cases they were never found to be constant, and the majority of cases show normal or even greater differences. Similar differences, greater than normal, are not infrequently observed in the high curves found in true diabetes, of