PHYSIOLOGY

Since the discovery of the blood-pressure-raising effect of extracts of the adrenal medulla in 1894 by Sir E. Sharpey-Schafer, a great deal of attention has been devoted to its physiology, but no such far-reaching effects have been accorded to the cortex. Apart from the production of virilism, the cortex is credited with a close association with lipid metabolism, being the storage organ for cholesterol fats.

It has been suggested that the cortex forms a precursor to epinephrin, but there is no valid reason to indicate that any mutual co-operation exists between cortex and medulla. There is, however, evidence that the cortex acts as a detoxifying agent. During the acute infections—streptococcal, diphtheria, and scarlet fever—the protoplasm of the cortical cells shows marked vacuolation and loss of lipoids, and it is thought that in this process the cholesterolin or cholesterolin esters saturate or inactivate poisons or toxins. Yet in starvation the lipid content of the cells remains unchanged.

Modern Conception of Gonadal Internal Secretions

A vast amount of experimental work has been devoted to the influence of the sexual glands, in an endeavour to explain the problem of the sexes. The bulk of this work emanates from the Continent, and the inquiry has been pursued from two aspects: (1) the grafting of sex glands; (2) the injection of extracts from the sex glands.

It is now accepted that every organism in its earliest development passes through an asexual stage, and that the soma reacts to maleness or femaleness by the specific action of the sexual hormones. This theory is supported by castration experiments in which the animal more or less loses its sex characters and tends to assume an asexual or neuter form. If a gonad is transplanted into a castrated animal of the other sex, the animal reacts to the former—that is, the hormones act as a sex specific. The most successful grafting experiments have been of this nature, for it has been found that there exists a certain antagonism between ovarian and testicular grafts on uncastrated animals, although simultaneous ovarian and testicular graft can produce experimental hermaphroditism, with variations in psycho-sexual behaviour. In these experiments it has not been possible to discount the interaction of the other endocrine glands. Thus, it has been possible to establish certain facts: (1) Formation and persistence of sex characters depend on sexual glands. (2) The formative and causative influence of the sexual glands do not relate to all sex characters. (3) The formative and causative influence of the sexual glands concern not only the sex characters involved in sex function—that is, genitals, heat, psycho-sexual behaviour—but characters in special relation to sex function—plumage, etc.

Internal Secretion of the Testis and Ovary

The clinical evidence available with regard to the testis shows that the interstitial cells are a necessary part of the testicular hormone, and there is no proof of an independent hormone elaborated by the cells of Sertoli or the tubules. With regard to the ovary, the position is less clear, and the endocrine function is intimately connected with processes taking place in the follicle. Consequently, all experimental results based on the injection of gonadal extracts have been conflicting and disappointing. This is not surprising considering the compound structure of the sexual glands, and the fact that we cannot control the rhythm of their normal function. Moreover, it has been found that the sexual hormones are not specific for each species. It is not until we can establish the quanti-

tative rate and rhythm of the secretory action of the gland that we can hope for more success from the injection of extracts.

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UNDULANT FEVER IN INFANCY

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During recent years sporadic cases of undulant fever have been recorded in these isles from time to time, and it would appear that they constitute only a small percentage of the cases which actually occur. There seems to be no question that the infection is spreading, and that what was formerly known as Mediterranean or Malta fever has been found in practically every country in Europe; it is also widespread throughout the United States. The causal organism, the *Brucella melitensis*, has been found in goats, cattle, horses, pigs, cats, and dogs, and the prevalence of animal infection in this country was shown by routine agglutination tests carried out at the Royal Veterinary College, London, in 1927-28, which returned positive results in 31.8 per cent. of 928 cows and heifers.

Sir W. Dalrymple-Champneys, in his report to the Ministry of Health on undulant fever, makes the statement that children under 5 years are almost exempt, and it is chiefly on this account, and because of our inability to find any previous record of a case in infancy in Britain, that we have made the following communication. As in the majority of cases described in this country, the causal organism was not isolated, but serologically and clinically there is no doubt that the following case was one of undulant fever.

R. H. B., male, aged 20 months, was in excellent health until July 30th, 1930, when a cold in the head developed. Following this there was vague ill-health, with loss of appetite, and the temperature became irregular, with recurrent attacks of pyrexia lasting about ten days, the highest figure being just over 102° F. With the fever there was diarrhoea, followed by constipation during the afebrile periods. Physical examination showed lymphoid hyperplasia in the posterior triangle of the neck, an easily palpable spleen, and definite enlargement of the liver. Despite the fever the patient looked quite fit throughout, and even during the pyrexial attacks was in no degree prostrated.

Three weeks after the onset the blood count was as follows: red cells 5,100,000 per c.mm., white cells 5,000 per c.mm. (small mononuclears 80 per cent., large mononuclears 4.7 per cent., polymorphonuclears 13.6 per cent., eosinophils 0.7 per cent., mast cells 1 per cent.); haemoglobin 60 per cent., and colour index 0.58. A second count, made on October 10th, during a febrile period, showed a rise in white cells to 14,125 per c.mm., 38 per cent. being large mononuclears, 20 per cent. small mononuclears, 14 per cent. hyalines, and 31 per cent. polymorphonuclears. The blood Wassermann reaction was negative, the urine was normal, while the Widal reaction for typhoid and paratyphoid A and B was also negative.

The nature of the infection was disclosed by a positive serum reaction to the *Brucella abortus* (Bang) up to a dilution of 1 in 250.

In investigating the source of infection we found

that the father of the patient was a dairy farmer at Brentwood, and he admitted that a somewhat higher percentage of abortion than usual had occurred among his cows. There was no history of ingestion of goat's milk. None of the family had been abroad. Three other cases of unexplained pyrexia in children from the same district were investigated, but in none could a positive serum reaction be obtained. The most recent report records that the patient is now in excellent health.

We are indebted to Dr. T. H. C. Benians and Dr. E. I. Clark for the pathological investigations which led to the diagnosis of the case.

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INFECTIONS AND INSULIN ACTION

OBSERVATIONS ON AN UNUSUAL CASE

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Sepsis and febrile infections are well known to antagonize insulin action in diabetics, so that the usual dose of insulin may have to be doubled or trebled. No adequate explanation of this fact has been produced, although two theories have been advanced to account for it:

1. The products of infection themselves destroy or inactivate the insulin in circulation. Such products may be bacterial toxins or more likely enzymes, such as trypsin,^{1 2} produced by leucocytes and pus. It is known that the ferments of pus cells³ destroy insulin *in vitro*, but this has not been proved to happen *in vivo*. This hypothesis may be called the theory of "chemical inactivation."

2. It has been suggested that the inhibition is due to the stimulation of the adrenal and thyroid glands⁴ by infections, and that it is their increased activity which antagonizes insulin action. This suggestion has been supported by some animal experiments, but the evidence is certainly not conclusive. This may be called the theory of "hormonal antagonism."

The case described below is very unusual, and supports the second theory. Increasing sepsis was accompanied by

diminished insulin requirements, the diminution coinciding with a failure of the patient's resistance and reaction to the infection.

DESCRIPTION OF THE CASE

A diabetic girl, aged 16, had been treated for two years with insufficient insulin. On admission to King's College Hospital in May, 1930, she was found to require 140 units a day on a diet of 80 grams carbohydrate, 67 grams protein, and 135 grams fat. She was therefore a very severe case, unusually "insulin resistant." She was a careless out-patient, and in August developed a large staphylococcal abscess in the thigh at the site of an insulin injection, a unique occurrence in our experience. This infection increased the insulin requirements for a week after the opening of the abscess. Healing was complete in three weeks, and she left hospital on a dosage of 140 units a day. In December, 1930, she developed a similar abscess in the upper arm, and her insulin requirements became 200 units a day. This was followed in ten days by another abscess near the shoulder-joint, and, in spite of free drainage, a succession of pyaemic abscesses appeared. Pure cultures of *Staphylococcus aureus* were obtained from them, and a positive blood culture in the fourth week. She died in the seventh week. At the post-mortem examination numerous abscesses were found throughout the body, and about 2 pints of pus in the pericardial sac. Until the end her appetite and digestion remained unimpaired, and the total quantity of the diet was kept unchanged. Frequent changes in insulin dosage were required, these being controlled by urine and blood sugar tests.

The pertinent features of her case, the insulin requirements, the average maximum temperature, and the white blood counts, are shown in the accompanying table. The two last are indications of her reaction to the infection. They show a gradual failure from the fourth week onwards; this was in keeping with the clinical appearance.