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.

After the second week the degree of sepsis and the amount of retained pus became progressively greater. The table indicates that her insulin requirements rose from 140 to 200 units at the onset of the infection, and fell progressively to 80 to 90 units as her resistance failed, in spite of an increase of the severity of the sepsis.

	Insulin Units	Temperature	White Blood Count
Before infection...	140	98.6°	
1st week	200	102.0°	
2nd week	200	103.0°	
3rd week	200	103.0°	29,000 per c.mm. Polymorphs 95 %
4th week	170	102.0°	31,000 per c.mm. Polymorphs 96 %
5th week	140	101.0°	13,000 per c.mm. Polymorphs 89 %
6th week	100	100.5°	11,000 per c.mm. Polymorphs 90 %
At 6½ weeks	90-80	99.0°	

DISCUSSION

As it is possible to exclude all the other factors which might have reduced her insulin requirements, we are forced to conclude that they depended on her progressive failure to react to her infection. Thus, while it is known that progressive emaciation may improve the diabetic condition, this was absent in her case. It was impossible to weigh her, but there was no visible reduction in her slight obesity, nor was there any failure to eat and absorb the usual total amount of food. Variations in her endogenous insulin production were very improbable, as she had been a very advanced diabetic showing no variation in her insulin requirements for the eight months during which she was under our observation. On the other hand, there was no change in the type of infection and no abatement of its severity as the insulin requirements grew less. The same bacteria, and presumably the same toxins and type of pus, were present in increasing quantities, and she should, if the theory of chemical inactivation be true, have required more insulin in the later weeks.

It seems fair to conclude, therefore, that it was not the sepsis or toxins *per se* which inhibited insulin action in the early stages of this case, but the reaction to them as manifested by a rise of temperature. When the latter failed, the insulin acted better. The febrile reaction seemed the determining factor, and it will be noted that the insulin diminished as soon as the average temperature began to fall, and before any change was seen in the blood count. Further evidence of the importance of a febrile reaction (as distinguished from a non-febrile infection) must have been noticed by insulin workers in comparing the effect of common colds in adults and in young children. The same degree of coryza (as far as we can judge) will cause pyrexia in a child, but not in an adult. The child requires more insulin; the adult does not, as a rule, unless he has a "feverish cold."

The above evidence associates the inhibition of insulin action directly with a febrile reaction, and only indirectly with the sepsis or infection producing the fever. Perhaps the explanation can be carried further, but not with any certainty, as too little is known of the mechanism producing fever. One hypothesis, however, explains the facts we have observed. Cramer⁵ advocates the view that a febrile reaction is produced by the stimulation of the adrenals and thyroid by infective agents, and has developed his arguments in a recent book, to which readers are referred. This would afford an adequate explanation of the inhibition of insulin, as it has been proved experimentally that the hormones of these glands, adrenaline and thyroxine, are direct antagonists to insulin.

Clinical evidence is also clear on the harmful effect of hyperthyroidism on diabetes, and also of conditions of nervous strain and excitement in which the suprarenal is stated, and may reasonably be presumed, to be over-active. If we grant in this case that the failing febrile reaction was due to an exhaustion of the adrenal-thyroid apparatus, it is easy to understand why the insulin requirements grew less in spite of increasing sepsis.

Unfortunately, even if the above hypothesis be true, it does not suggest any therapeutic measure in infections other than an increase of insulin. We have tried ergotamine,⁶ a sympathetic depressant, which in theory should be ideal, and, indeed, in practice augments insulin action, but its toxic properties have shown it to be undesirable.

SUMMARY

An unusual case of septicaemia in a diabetic is reported in which the insulin requirements, after an initial increase, became progressively less as the sepsis grew worse. This reduction coincided with a falling temperature and failure of reactive powers. It is suggested that the inhibition of insulin action by sepsis is not directly due to the sepsis or toxins, but to the accompanying febrile reaction. It is further suggested that this reaction may be due to the increased activity of the adrenal and thyroid glands, recognized antagonists to insulin. If their reaction fails or diminishes, as in this case, then the antagonism to insulin is removed, and the dose required becomes less, in spite of increasing sepsis.

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Memoranda

MEDICAL, SURGICAL, OBSTETRICAL

KERATITIS PUNCTATA SUPERFICIALIS

From the number of cases of keratitis punctata superficialis that one formerly came across it could not, I think, have been termed a common ocular affection, yet the number of cases I saw during the past winter leads me to believe that it is now of much commoner occurrence than might be expected. It is a condition very easily missed, and one not likely to be found unless carefully looked for. Practically all the recent cases have been mistaken for, and treated as, a conjunctivitis. This is owing to the fact that the conjunctiva shows a mild hyperaemia of both its palpebral and conjunctival portions; there is no true discharge, as is present in conjunctivitis, but an excess of tears. The pain is of a gritty, burning nature, and more severe than would be encountered in a conjunctivitis of so mild a degree. There is also considerable photophobia, which is far more pronounced and distressing than in a case of conjunctivitis.

If the cornea is examined with an ordinary light nothing abnormal is seen, but with focal illumination and a magnifying glass, particularly if the pupil is dilated, the surface of the cornea will be seen to be cloudy and scattered over with several minute grey dots, the numbers of which vary considerably. They may be arranged in groups or rows, and are very much more abundant in the centre, the periphery of the cornea being often quite clear. If fluorescein is instilled into the conjunctival sac some of the spots are stained green, but others remain unaffected. An examination with the corneal microscope shows the spots to be of a superficial nature, involving