

wards. Thus, we do not consider the number of children with "sensitivity" manifestations as any accurate indication of the real number of cases. Clinical or radiological evidence of the primary infection was present at some time in 80% of the children traced.

But we do think that the number of cases of miliary dissemination, bone disease, or meningitis is likely to reflect the risk of these complications in the children infected at the age of less than 5 years. Thus in 1020 infected children 16 (1.5%) developed bone lesions (4 of these after treatment for either tuberculous meningitis or miliary tuberculosis) and 42 (4.1%) meningitis or miliary tuberculosis or both, within a minimal period of observation of two years. If the possible range is calculated, we find that the risk is 1-2% for bone disease and 2.9-5.5% for either tuberculous meningitis or miliary tuberculosis. We would have liked to be able to take our data further and to calculate the risk in children infected before and after the age of 2 years. Certainly 31 of the 42 cases of miliary tuberculosis or of tuberculous meningitis occurred in children infected before the age of 2 years, but we did not know if the remaining 11 had been infected before or after their second birthday. If we assumed that all the 11 had been infected afterwards, the calculated risks of the development of tuberculous meningitis or miliary were 1 in 20 at the age of less than 2 years and 1 in 30 at the age of more than 2 years, but this difference was not statistically significant.

COMMENT

The chances of developing bone lesions, miliary tuberculosis, or tuberculous meningitis are the greatest hazards following the primary infection with tuberculosis. It is therefore important that these risks should be measured, and we can only assume that they are not well known because the conditions for their measurement are difficult to obtain.

All writers on childhood tuberculosis are agreed that the risk of illness is greatest with infection in the first year of life, remains high until the age of 2 or 3 years, and then diminishes. Authors who have followed large series of children infected in the first year or two presenting in hospital clinics or outpatient departments have found a varying mortality, usually about 10-20% of children within five years (Bernard et al. 1925, Asserson 1927, Myers and Kernkamp 1930, Wallgren 1938, Brailey 1940). In the Luebeck disaster, which combined heavy oral infection with extremely young age, there was a mortality of 36% (72 from 251) within a year.

None of these investigations, however, represents the risk of development of these lesions in all children infected in a given population under natural conditions. We have only been able to find one estimate similar in method to ours. Holmdahl (1950), in a follow-up designed to study the prognosis in children who had erythema nodosum at the time of primary infection, found that in children aged less than 7 years there was a 2.9% chance of the development of either tuberculous meningitis or miliary tuberculosis within a year of infection, and 3.8% within two years. After two years the risk did not increase.

It does appear, therefore, that primary infection with tuberculosis in children aged less than 5 years carries a risk of the development of serious complications of about 3-5%. This risk is probably not the same for all children aged less than 5 years and is likely to vary with age at infection, and possibly with other factors, such as genetic resistance, with repeated exposures or the development of other infections. As yet we have not the data to make any numerical estimate of these factors.

SUMMARY

The known rate of conversion in a group of children representative of the childhood population of a city has

been used to estimate the number of primary infections in children aged less than 5 years.

4% of all children aged less than 5 years were infected—1020 from a population of 25,000.

We traced 258 of these children and found that, within a minimum of two years from infection, 16 (1.5%) had developed lesions of bone and 42 (4.1%) had developed either tuberculous meningitis or miliary tuberculosis; and that 36 (3.5%) had died of tuberculosis.

We wish to thank all our friends, and acknowledge the great help we have received in this study, particularly from the chest physicians of the clinics in Newcastle, and the medical staffs of the children's hospitals.

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INFLUENCE OF CARBOHYDRATE METABOLISM ON BACTERIAL ALLERGY ITS RELATION TO CORTISONE DESENSITISATION

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HYPERSENSITIVITY to streptococcal allergens, ascorbic-acid deficiency persisting into convalescence, and endocrine disturbance have all been suspected of playing significant parts in the pathogenesis of rheumatic fever. Based on this broad analogy, a study has been made of bacterial allergy (as represented by sensitivity to tuberculin in B.C.G.-infected guineapigs), ascorbic-acid deficiency, and the effects of various hormones upon them (Long and Miles 1950, Long et al. 1951a, b, and c, Cornforth and Long 1952). The limitations of animal experiments in elucidating human pathology have been repeatedly stressed (Long 1951, 1952). Our present views, to which these limitations strictly apply, may be summarised as follows.

It has been postulated that, in B.C.G.-infected guineapigs, cortisone and alloxan facilitate the formation of dehydroascorbic acid (Long et al. 1951c), which, by inhibiting phosphoglucomutase, blocks the conversion of glucose-1-phosphate to glucose-6-phosphate—accumulation of glucose-1-phosphate being associated with diminished sensitivity to tuberculin (fig. 1) (Cornforth and Long 1952). Organic phosphates representing the various stages of carbohydrate metabolism were therefore tested empirically. Among these, adenosine diphosphate (A.D.P.) was shown to have marked desensitising activity, whereas in comparable doses the closely related adenosine triphosphate (A.T.P.) had none (Cornforth and Long 1952).

It is known that the breakdown of glycogen in the tissues (leading in the first stage to glucose-1-phosphate) is sensitive to the equilibrium between A.T.P. and A.D.P., and to the availability of inorganic phosphate. This has been emphasised by Potter (1944), who says: "It must be recognised that there is a basal rate of A.T.P. breakdown which is balanced by the resting metabolism, and that glycogen may be expected to break down only when there is a sudden shift in the A.T.P./A.D.P. balance." These observations refer to intracellular metabolism, but it is possible that such arguments based on intracellular physiology may apply in the tuberculin-sensitive

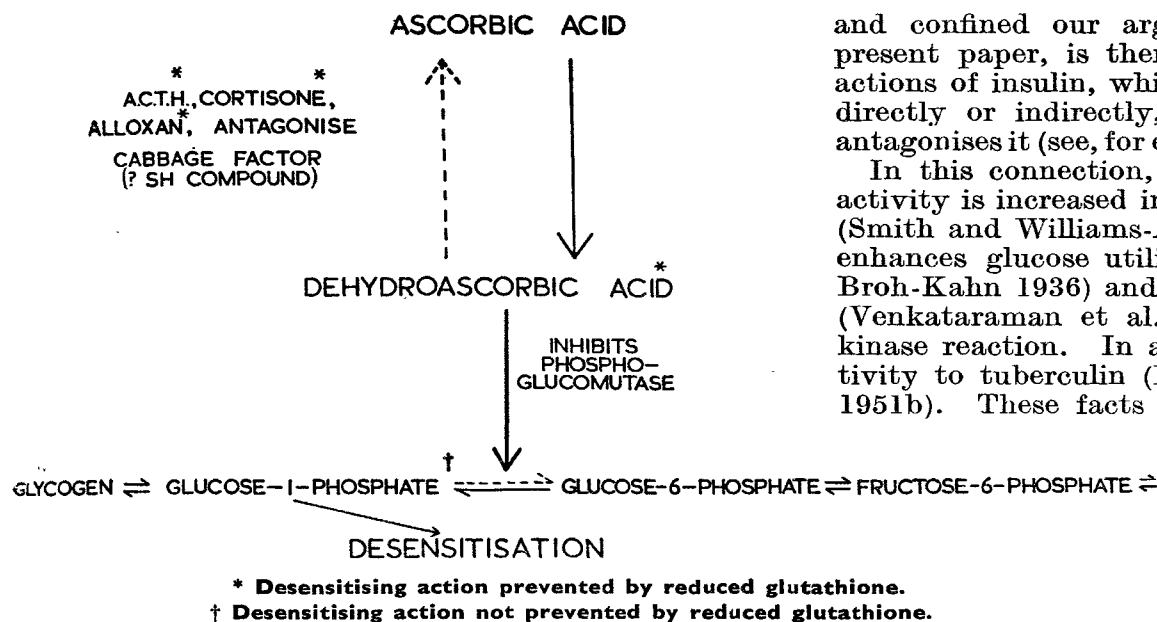


Fig. 1.

guineapig to the actions of metabolites injected extracellularly; that the extracellular injection of A.D.P. may cause glycogen to be converted to glucose-1-phosphate and so diminish sensitivity; and that the simultaneous extracellular injection of A.T.P. and A.D.P., by preventing a shift in the A.T.P./A.D.P. balance, may prevent desensitisation.

In the present paper we show that, as the ratio of extracellularly injected A.T.P. to A.D.P. is increased, the desensitising action of A.D.P. is first diminished and then abolished; in addition, injected A.T.P. inhibits the desensitising action of alloxan, cortisone, and dehydroascorbic acid, but not that of glucose-1-phosphate. These facts are consistent with our hypothesis; for if A.T.P. has inhibited glycogen breakdown, blocking phosphoglucumutase will not increase the concentration in the tissues of glucose-1-phosphate. On the other hand, the concentration, and therefore the desensitising action, of injected glucose-1-phosphate will be independent of these factors. Thus the results we expected on the basis of intracellular metabolism were achieved. It seems more probable that these organic phosphates, injected extracellularly into tuberculin-sensitive guineapigs, influence normal intracellular carbohydrate metabolism than that they produce a hypothetical series of pharmacological coincidences associated with like effects. Glucose-1-phosphate is a normal metabolite, but its rôle as intermediate in an important biological process may mean that, unless the balance of the process is appropriately disturbed, it is never free from the enzyme complex; so even minute quantities introduced from outside may produce an effect out of proportion to the total amounts involved in glycogen metabolism. It is possible that cell permeability is increased in guineapigs undergoing a severe tuberculin response, and that the argument holds only for this condition. However, we conclude that in B.C.G.-infected guineapigs, glycogenolysis (glycogen breakdown), with resulting glucose-1-phosphate formation, is associated with diminished sensitivity to tuberculin; that injected A.T.P., by stimulating glycolysis (glucose breakdown) and inhibiting glycogenolysis, antagonises this action and so prevents desensitisation; and therefore, that hexokinase hyperactivity and hypersensitivity on the one hand, and hexokinase hypoactivity and desensitisation on the other hand, are associated phenomena.

Fortunately, the actions of certain hormones upon carbohydrate metabolism in general, and upon hexokinase activity in particular, are not subject to the restrictions imposed by these problems of intracellular-extracellular relationship which have hitherto handicapped

and confined our argument. The latter part of the present paper, is therefore devoted to a study of the actions of insulin, which stimulates hexokinase activity directly or indirectly, and of growth hormone, which antagonises it (see, for example, Wright 1952, Young 1948).

In this connection, it is noteworthy that hexokinase activity is increased in the tissues of thyrotoxic animals (Smith and Williams-Ashman 1951), and that thyroxine enhances glucose utilisation in the tissues (Mirsky and Broh-Kahn 1936) and stimulates the formation of A.T.P. (Venkataraman et al. 1950), which initiates the hexokinase reaction. In addition, thyroxine increases sensitivity to tuberculin (Long and Miles 1950, Long et al. 1951b). These facts are consistent with, and support, our present contentions.

The argument is strengthened by our findings (reported here) that growth hormone, which inhibits hexokinase activity, depresses sensitivity to tuberculin, whereas insulin, which stimulates hexokinase activity, antagonises the desensitising actions of cortisone, alloxan, and dehydroascorbic acid, but not of glucose-1-phosphate. Moreover, the compensatory phase that follows insulin hypoglycaemia—a phase for which the adrenal cortex is largely responsible (see, for example, Wright 1952)—is associated with desensitisation. As might be expected, this compensatory phase of desensitisation, like that produced by cortisone, does not occur in animals previously injected with reduced glutathione nor in ascorbic-acid-deficient guineapigs (cf. Long et al. 1951a and c). In addition, it can, like cortisone desensitisation, be prevented by injected A.T.P. In this connection, the observation of Kersley et al. (1951) that insulin hypoglycaemia is succeeded in rheumatoid arthritis by symptomatic relief comparable to that obtained with adrenocorticotrophic hormone (A.C.T.H.) is noteworthy.

From our experiments with organic phosphates and hormones, we conclude that sensitivity to tuberculin in B.C.G.-infected guineapigs depends on a balance between hexokinase-stimulating and hexokinase-depressing hormones, with the adrenal cortex controlling the metabolic process most intimately linked with sensitivity—namely, the concentration in the tissues of glucose-1-phosphate. Although part of the argument is based on results obtained with extracellularly injected carbohydrate metabolites, the remainder and major part is not subject to this limitation, and yet points to the same conclusions.

METHOD

Albino guineapigs of the Hampstead strain, weighing 350–550 g. and fed on a pelleted diet (Bruce and Parkes 1947) supplemented with unlimited cabbage, were injected with B.C.G. vaccine, and sensitivity to tuberculin was estimated by the method of Long and Miles (1950).

All drugs tested, except glutathione, growth hormone, cortisone acetate, and insulin, were dissolved in 1 ml. of normal saline and injected subcutaneously two hours before the tuberculin. Reduced glutathione was dissolved in gas-free distilled water and adjusted with sodium bicarbonate solution to pH 6; approximately 150 mg. per kg. body-weight, in a volume of 2 ml., was injected intraperitoneally two hours before the tuberculin. Cortisone acetate was suspended in 1 ml. of normal saline and injected six hours before the tuberculin. Growth hormone, partly dissolved, partly suspended, in 1 ml. of normal saline, was injected in the doses, and at the time-intervals, detailed in the experiments. Insulin was dissolved in 1 ml. of normal saline and injected subcutaneously at the time-intervals detailed in the experiments; the batch did not contain detectable quantities of hyperglycaemic factor. Animals treated with insulin received no food on the day of the experiment.

As in previous work, the diameter of the tuberculin lesions after twenty-four hours was found to be proportional to the logarithm of the dose of tuberculin; and it was possible to estimate the degree of sensitivity by the relative positions of the dosage-response lines fitted to the mean lesion-diameters plotted against the logarithm of the dose. Changes in sensitivity are measured in terms of the change in potency of standard doses of tuberculin compared with that in control animals. Thus a potency ratio of 0.25 indicates a fourfold decrease, of 4.00 a fourfold increase in sensitivity. The probability that ratios differing from unity indicate a significant change in sensitivity is expressed by the

TABLE I—ANALYSIS OF RESULTS OF EXPERIMENTS

Expt.	Agent and dose per kg. body-weight	Variance ratio*	P	Potency ratio
1.	A.T.P. (10 mg.) + A.D.P. (2 mg.) A.T.P. (2 mg.) + A.D.P. (2 mg.) A.T.P. (1 mg.) + A.D.P. (2 mg.)	< 1 27.59 56.54	— < 0.001 < 0.001	0.925 0.464 0.252
2.	A.T.P. (10 mg.) Alloxan (50 mg.) Alloxan (50 mg.) + A.T.P. (10 mg.) Cortisone acetate (5 mg.) Cortisone (5 mg.) + A.T.P. (10 mg.) Dehydroascorbic acid (50 mg.) Dehydroascorbic acid (50 mg.) + A.T.P. (10 mg.) Glucose-1-phosphate (0.01 mg.) Glucose-1-phosphate (0.01 mg.) + A.T.P. (10 mg.)	< 1 75.05 — 79.81 — 17.81 60.04 — 162.42 182.46	— < 0.001 — < 0.001 — < 0.001 < 0.001 — < 0.001 < 0.001	1.09 0.423 — 0.912 0.462 1.434 0.519 — 1.000 0.325 0.312
3.	Insulin (2 units) injected 0 hours before tuberculin Injected 2 hours before tuberculin Injected 4 hours before tuberculin Injected 6 hours before tuberculin Insulin (2 units) in ascorbic-acid-deficient guineapigs, injected 6 hours before tuberculin Insulin (2 units) injected 6 hours before tuberculin + reduced glutathione (150 mg.) Insulin (2 units) injected 6 hours before tuberculin + A.T.P. (10 mg.)	2.14 7.42 18.99 49.18 5.03 1.26 43.07	> 0.10 < 0.05 < 0.001 < 0.001 > 0.05 > 0.20 < 0.001	1.23 0.596 0.500 0.458 1.445 1.18 2.06
4.	Alloxan (50 mg.) Alloxan (50 mg.) + insulin (2 units) Cortisone acetate (5 mg.) Cortisone + insulin (2 units) Dehydroascorbic acid (50 mg.) Dehydroascorbic acid (50 mg.) + insulin (2 units) Glucose-1-phosphate (0.01 mg.) Glucose-1-phosphate (0.01 mg.) + insulin (2 units)	51.28 < 1 92.03 9.38 84.97 < 1 53.02 61.38	< 0.001 — < 0.001 < 0.05 < 0.001 — < 0.001 < 0.001	0.466 1.182 0.295 1.953 0.249 1.034 0.366 0.364
5.	Growth hormone (10 mg. per kg.) injected 0 hours before tuberculin Injected 3 hours before tuberculin Injected 9 hours before tuberculin Injected 12 hours before tuberculin Growth hormone (10 mg.) at 0 hours + cortisone acetate (5 mg.) Cortisone acetate (5 mg.)	3.47 129.07 214.07 559.11 270.17 25.24	> 0.05 < 0.001 < 0.001 < 0.001 < 0.001 < 0.001	0.733 0.14 0.08 0.04 0.084† 0.545
6.	Growth hormone (10 mg.) injected 6 hours before tuberculin Growth hormone (10 mg.) + A.T.P. (5 mg.) Growth hormone (10 mg.) + reduced glutathione (150 mg.) Growth hormone (10 mg.) + insulin (2 units) Growth hormone (10 mg.) in ascorbic-acid-deficient animals	163.35 111.09 171.94 81.52 51.82	< 0.001 < 0.001 < 0.001 < 0.001 < 0.001	0.279 0.346 0.287 0.332 0.253

* Ratios of "between treatments" variance to error variance.

† Cortisone acetate + growth hormone produced effects significantly greater than either alone.
Alloxan + growth hormone also produced an effect significantly greater than either alone.
These synergistic effects did not occur in ascorbic-acid-deficient guineapigs.

TABLE II—CONDITIONS IN WHICH DESENSITISATION DEVELOPED WITH THE AGENTS TESTED

Agent and dose per kg. body-weight	Normal diet	Ascorbic-acid deficient diet	Reduced glutathione (150 mg. per kg.)	A.T.P. (10 mg. per kg.)	Insulin (2 units per kg.)
Alloxan (25–50 mg.) ..	+	—	—	—	—
Cortisone acetate (5 mg.) ..	+	—	—	—	—
Dehydroascorbic acid (50 mg.) ..	+	+	—	—	—
Glucose-1-phosphate (0.01 mg.) ..	+	+	+	+	+
Growth hormone (10 mg.) ..	+	+	+	+	+
Insulin (2 units) (compensatory phase succeeding hypoglycaemia) ..	+	—	—	—	*

+ = desensitisation. — = no desensitisation.
* Sensitivity significantly greater than in controls.

value of P in the tables. Ratios for which P is 0.05 or less are considered significant.

RESULTS

Adenosine Triphosphate

The A.T.P. used in these experiments contained a small proportion of A.D.P. which was taken into account when calculating the amounts of the two substances.

The simultaneous injection of A.T.P. (1 mg. per kg. body-weight) and A.D.P. (2 mg. per kg.) caused a significant fourfold diminution in sensitivity; this effect was halved when the dose of A.T.P. was doubled, and abolished by a tenfold increase (experiment 1, table I). Thus, by increasing the ratio of A.T.P. to A.D.P., desensitisation was prevented.

The injection of A.T.P. (10 mg. per kg.) did not in itself influence sensitivity, but in cortisone-treated animals (5 mg. per kg.), it not only abolished but significantly increased sensitivity to tuberculin; however, it merely abolished the desensitising action of alloxan (50 mg. per kg.) and dehydroascorbic acid (50 mg. per kg.), and it did not influence that of glucose-1-phosphate (0.01 mg. per kg.) (experiment 2). These results, excluding the marked hypersensitivity in animals treated with both cortisone and A.T.P., had, as already stated, been expected. The explanation of these effects may perhaps be inferred by considering the mechanism by which A.T.P. may inhibit glycogen breakdown. Stimulation of the hexokinase reaction by A.T.P. leads to the disappearance of inorganic phosphate, fixed during the later oxidative stages of glycolysis. Cori and Cori (1940) showed that, when the ratio of inorganic phosphate to glucose-1-phosphate falls below a certain level, glycogen splitting (i.e., production of glucose-1-phosphate) ceases and glycogen synthesis occurs. The reason for the special effect of cortisone may be that (unlike alloxan or dehydroascorbic acid) it induces synthesis of glucose from protein. Fuel is thus provided for the hexokinase reaction, and more inorganic phosphate disappears. Some of the glucose mobilised by cortisone is known to be converted through glucose-1-phosphate to glycogen; but in the special circumstances under discussion this should not cause accumulation of glucose-1-phosphate, the concentration of which would remain low so long as there was a shortage of inorganic phosphate.

Insulin

Insulin (2 units per kg. body-weight) injected at the same time as the tuberculin (0 hours) did not significantly influence sensitivity; but injected four or six hours beforehand, it markedly depressed sensitivity (experiment 3). This experiment was repeated and tuberculin sensitivity was plotted against blood-sugar levels (fig. 3): as hyperglycaemia succeeded hypoglycaemia, sensitivity

fell. This compensatory hyperglycæmic phase is attributable to hyperactivity of adrenal cortex and medulla (see, for example, Wright 1952), and consistent with this view, the desensitisation associated with it did not occur in guineapigs previously injected with reduced glutathione, or in ascorbic-deficient animals (experiment 3) (cf. Long et al. 1951a and b). It is noteworthy that, as in cortisone-treated animals, injected A.T.P. caused a significant increase in sensitivity (experiment 3) (table II).

The immediate effect of insulin, during the phase of hypoglycæmia, is shown consistently by a slight increase in sensitivity. In only one experiment was this increase statistically significant; the result given in experiment 3 is typical. Insulin, by stimulating hexokinase activity and increasing glycogen storage, might be expected, on the basis of our hypothesis, to antagonise desensitisation by cortisone, alloxan, and dehydroascorbic acid. Insulin is thought to stimulate phosphorylase and so promote the conversion of glucose-1-phosphate to glycogen (see, for example, Young 1948). Such an effect was not apparent in our experiments, extracellularly injected glucose-1-phosphate proving fully active in animals treated with insulin (experiment 4). Insulin prevented desensitisation by alloxan and dehydroascorbic acid, and significantly increased sensitivity in cortisone-treated animals (experiment 4) (table II).

Presumably this effect, like that of A.T.P. under similar conditions, is due to the hexokinase-stimulating activity of insulin, reinforced by glucose derived from protein under the influence of cortisone.

Growth Hormone

Growth hormone antagonises insulin and depresses hexokinase activity (see, for example, Young 1948). It proved a powerful desensitising agent in a dose of 10 mg. per kg. body-weight, increasing in effectiveness up to twelve hours, beyond which time it was not tested. In cabbage-fed but not in ascorbic-acid-deficient guineapigs, it had a synergistic action with cortisone and also alloxan (experiment 5). The desensitising action of growth hormone is not influenced by injected A.T.P., reduced glutathione, or insulin; or by ascorbic-acid deficiency in the diet (experiment 6) (table II), all of which, as already stated, prevent cortisone desensitisation. The experiments quoted here were carried out with a single large batch of growth hormone provided by Messrs. Armour; they were confirmed with a highly purified preparation provided by Prof. F. G. Young. This latter preparation, tested at eight hours, had approximately twice the desensitising potency of the

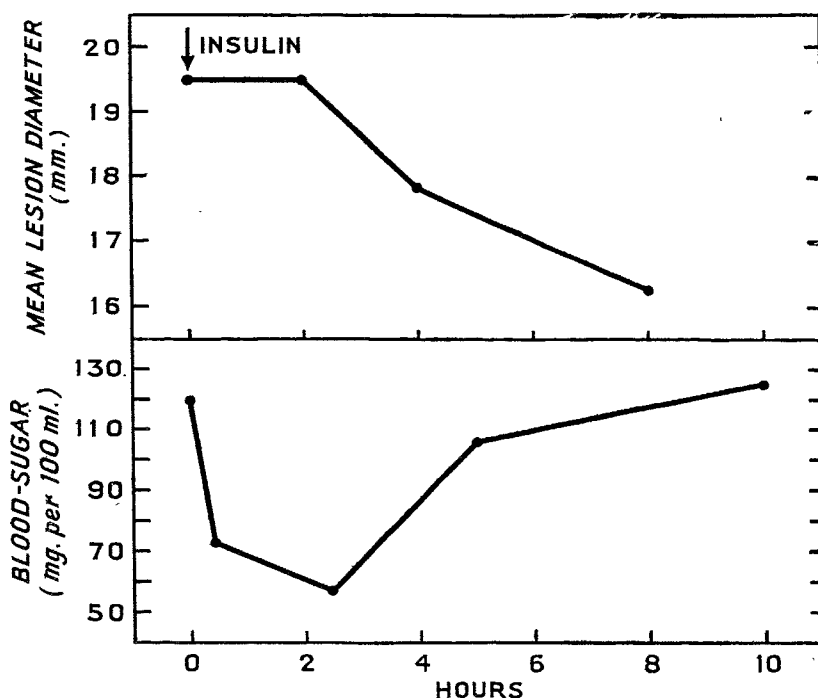


Fig. 3—Effect of insulin on blood-sugar level and tuberculin hypersensitivity.

Armour preparation, possibly owing to its greater solubility.

DISCUSSION

The idea that insulin, the adrenal steroids, and growth hormone influence hexokinase activity is not new. The Cori suggested, on a basis of in-vitro experiments, that the adrenal steroids and the anterior pituitary inhibit hexokinase activity, and that insulin antagonises the actions of these hormones and so allows hexokinase activity to be resumed (Cori and Cori 1946, Colowick et al. 1947). But the Cori contentions are at variance with the facts. Excess of anterior pituitary and adrenocortical hormones are known to influence blood-sugar in a manner comparable to that associated with insulin deficiency. But insulin, which would be expected from the Cori hypothesis to be inactive in the hypophysectomised or adrenalectomised animal, shows instead enhanced activity. It seems improbable that adrenal steroids, in times of emergency, would stimulate the formation of glucose from protein, only to block its oxidation and moreover the oxidation of glucose from other sources. The idea that growth hormone inhibits hexokinase activity is more acceptable and does not depend only on in-vitro evidence. Growth hormone

increases the formation of tissue protein, a process associated with a decrease in the amount of amino-acids in the blood and a decrease in nitrogen excretion in the urine; serum alkaline phosphatase and cell lipids are increased in amount, but reserve fat is decreased; calcium and phosphate retention are associated with growth of bone.

These build-up processes, particularly of protein, depend upon the maintenance of a normal level of blood-glucose. If this level falls, adrenal steroids facilitate protein conversion to glucose; thus growth hormone, by blocking hexokinase activity, would be expected to maintain the blood-sugar level, prevent protein breakdown, and assist growth. In the present paper, we show that the desensitising actions of growth

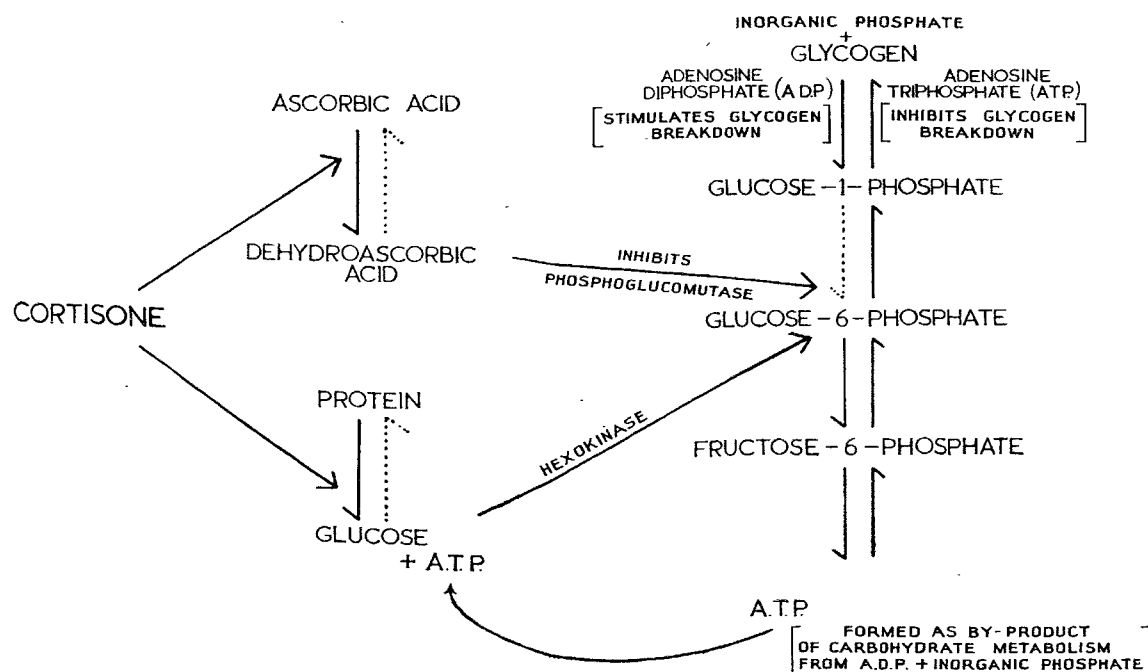


Fig. 2.

hormone and of cortisone are brought about by different and synergistic mechanisms. Their site of action is therefore likely to be different. We suggest that, in contrast to the action of cortisone, growth hormone blocks hexokinase activity, and that under its influence the body relies for its energy to a greater extent upon glycogen breakdown, associated with glucose-1-phosphate formation. This would explain the synergistic effect of growth hormone with both cortisone and alloxan, since blocking phosphoglucomutase in an animal which is breaking down glycogen will cause an accumulation of glucose-1-phosphate and also oppose A.T.P. formation.

SUMMARY

Using the response to intradermal tuberculin as a measure of allergic hypersensitivity in albino guineapigs injected with B.C.G., we find that:

(1) Single subcutaneous injections of adenosine diphosphate diminish sensitivity. This desensitising action is first diminished and then abolished by the simultaneous injection of increasing amounts of adenosine triphosphate.

(2) Single subcutaneous injections of adenosine triphosphate prevent desensitisation by alloxan, cortisone acetate, and dehydroascorbic acid. They do not influence desensitisation by glucose-1-phosphate.

(3) Single subcutaneous injections of adenosine triphosphate not only abolish desensitisation by cortisone acetate but actually increase hypersensitivity.

(4) Single subcutaneous injections of insulin do not in themselves significantly influence sensitivity. The compensatory phase that succeeds insulin hypoglycaemia is associated with desensitisation.

(5) The desensitisation that succeeds insulin hypoglycaemia is thought to be due to naturally liberated cortisone, since it does not occur in ascorbic-acid-deficient animals, is prevented by injection of reduced glutathione, and is intensified by injection of adenosine triphosphate.

(6) Single subcutaneous injections of insulin prevent desensitisation by alloxan and dehydroascorbic acid; they not only prevent desensitisation but intensify sensitivity in animals treated with cortisone acetate; and they are without effect on the desensitising action of glucose-1-phosphate.

(7) Single subcutaneous injections of growth hormone depress sensitivity to tuberculin. This action was unaffected under our experimental conditions by injection of reduced glutathione, A.T.P., or insulin, or by ascorbic-acid deficiency.

(8) In desensitisation, growth hormone (given in single subcutaneous injections) has a synergistic action with either cortisone acetate or alloxan.

Our present hypothesis (see fig. 2) provides a convenient summary of these facts. We have previously suggested that cortisone facilitates the oxidation of ascorbic acid to dehydroascorbic acid, which inactivates phosphoglucomutase, and thus blocks glycogen breakdown and increases the tissue concentration of glucose-1-phosphate—which is intimately concerned with desensitisation. We now suggest that adenosine triphosphate and insulin oppose this desensitisation by stimulating hexokinase activity, leading to a disappearance of inorganic phosphate which would otherwise be used for glucose-1-phosphate formation from glycogen. This effect is actually enhanced by the glucose formed from protein under the influence of cortisone, more glucose being thus provided for the hexokinase reaction.

The desensitisation produced by adenosine diphosphate and by growth hormone is ascribed to the effect of these substances in causing breakdown of glycogen to glucose-1-phosphate; with the hormone, at least, this effect is considered to be due to inhibition of hexokinase activity.

We are indebted to Dr. Knud Tolderlund of the State Serum Institute, Copenhagen, for the B.C.G.; to Messrs. Armour, of Chicago and London, for a generous gift of growth hormone; to Dr. A. Morrison, of Roche Products Ltd.,

Hertfordshire, for alloxan, dehydroascorbic acid, and reduced glutathione; to our colleague Dr. R. Porter for the insulin; and to Prof. F. G. Young, F.R.S., for some highly purified growth hormone.

We are greatly indebted to Miss M. V. Mussett for statistical analyses not only on the experiments described here but also on a large number of unquoted confirmatory experiments on which these observations are based.

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THE PREVENTION OF POSTOPERATIVE PULMONARY ATELECTASIS *

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IN the forty years since postoperative pulmonary atelectasis was recognised by William Pasteur at the Middlesex Hospital (Pasteur 1908, 1910) there has been little change in the incidence of this complication despite advances made in surgery and anaesthesia and the introduction of antibiotics.

The prevention and treatment of this condition is important because atelectatic areas readily become infected, leading to bronchopneumonia (Coryllos 1929, 1930).

Segmental atelectasis is the common postoperative pulmonary abnormality and it was found in 94% of patients who developed pulmonary complications after abdominal operations (Palmer 1952). It results from occlusion of the smaller bronchi by retained secretion and the absorption of air distal to the block (Coryllos 1929, 1930). The lesion is commonly basal and unilateral, but it may be bilateral and involve segments of the middle lobe or lingula (Palmer and Sellick 1952b).

We describe here a method for the prevention of postoperative atelectasis. It is based on the hypothesis that, if the factors which favour the retention of sputum in patients after operation can be overcome, atelectasis should seldom occur.

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Table I shows that the many factors concerned in the production of atelectasis ultimately have their effect by causing retention of sputum. We consider that a deficient expulsive mechanism, a reduction in bronchial calibre, and qualitative or quantitative changes in the bronchial secretion are all of great importance.

The cough reflex is the mechanism by which excess secretion is normally removed from the large bronchi (Ballon 1939, Bullowa 1944). After abdominal operations coughing is restricted owing to pain from the wound, and the cough is rendered weak and ineffective by the semirecumbent posture, impaired diaphragmatic move-

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