Insulin Response during Tularemia in Man

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SUMMARY

Serum insulin concentrations were measured serially in seven nondiabetic subjects following a rapid intravenous glucose load during a preinfection control period, during early clinical respiratory tularemia, and again in convalescence following therapy. Within twenty-four hours of onset of clinical illness the rate of glucose disappearance from the blood had diminished significantly ($p<0.05$). At the same time there was a brisk rise in insulin levels reaching higher peak concentrations and falling more slowly than the response observed during the preinfection control period. The pattern during clinical illness was different from that described after intravenous glucose loading in maturity onset diabetes or obesity and may have been influenced by glucocorticoid excess. Increased whole blood pyruvate concentrations following glucose loading during clinical illness were compatible with heightened glucocorticoid action. The magnitude of insulin response during clinical illness was significantly increased ($p<0.02$) and was directly related to height of fever. In contrast, the rate of glucose disappearance was inversely related to fever. The inverse relationship of the magnitude of insulin output to the rate of glucose disappearance suggested a peripheral inhibition of insulin action during infection. Although fever may have played a role during acute illness, the persistence of an abnormal insulin response in one patient during convalescence suggested that this change was not dependent upon fever alone. Other factors that may have contributed to the peripheral inhibition of insulin action during clinical illness are briefly discussed. DIABETES *16*:369-76, June, 1967.

Carbohydrate metabolism is adversely influenced by infection. Glycosuria was detected in cholera patients over a hundred years ago and has been reported many times since during a variety of infectious diseases.[1,2] The need for increased doses of insulin in the diabetic patient with superimposed infection is well recognized, but the pathogenesis of progressive deterioration of diabetic control,[3] which may begin before the onset of clinical illness, is poorly understood. Even the nondiabetic patient has an increased fasting blood sugar concentration and impaired glucose tolerance during generalized infection.

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Circumstantial evidence[2-10] has implicated a number of factors which might contribute to altered carbohydrate metabolism during infection. Diminished insulin production secondary to impaired beta cell function,[3] inhibition of pancreatic insulin release,[3] increased enzymatic destruction of insulin,[4] or an increased binding of insulin by antibody[5] could contribute directly to reduced insulin activity during infection. Other hormonal effects,[6,7] such as depletion of glycogen stores, gluconeogenesis, fatty acid mobilization, or suppression of glycogen-synthesizing enzymes in the liver may in themselves alter peripheral pathways of carbohydrate metabolism or may serve to antagonize the peripheral action of insulin. Since actual measurements of insulin response to a glucose load have not previously been obtained during infection, information with which to support or reject these possibilities has been lacking. Prospective studies in nondiabetic subjects were therefore undertaken to determine whether the insulin response was altered during acute infectious illness.

METHODS AND MATERIALS

Seven healthy males with no family history of diabetes and no prior exposure to exogenously administered insulin were selected from a group of volunteers exposed to respiratory tularemia.*

Respiratory tularemia was produced by inhalation of approximately 25,000 viable *Pasteurella tularensis* organisms.[11-13] Following an incubation period of twenty-four to seventy-two hours the clinical spectrum of illness in the seven patients ranged from a mild headache and malaise without fever to a systemic response characterized by myalgia, photophobia, and rectal temperatures reaching 104° F. Febrile patients were treated within twenty-four hours of the onset of symptoms

*This study, conducted under the sponsorship of the Commission on Epidemiological Survey, Armed Forces Epidemiological Board, was an incidental part of continuing long-term investigations of vaccine efficacy and diagnostic and therapeutic methods in infectious illnesses. Prior to volunteering for the study, all participants were informed in detail concerning the purpose, procedures, and risks involved (AR 70-25).

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with streptomycin, 1 gm. twice daily for seven days. Within forty-eight hours of institution of therapy the temperatures became normal, and by seventy-two hours the patients were asymptomatic. One subject who remained afebrile throughout his hospital course was started on therapy when he developed headache and nausea five days after exposure. Elevation of agglutination titers to *P. tularensis* which served to confirm the occurrence of infection, were recorded in all patients three weeks after exposure.

Intravenous (IV) glucose tolerance tests were performed prior to exposure, during fever but before institution of therapy, and in convalescence two weeks later at a time when all patients were afebrile and asymptomatic. Glucose tolerance was studied in the afebrile subject immediately before institution of therapy. The intravenous route of glucose administration was chosen to avoid possible variations in gastrointestinal absorption, to avoid stimulation of an intestinal glucagon response, and to provide an exactly timed stimulus for insulin response.

Following acquisition of a fasting blood sample, 300 ml. of 20 per cent glucose in distilled water were given by vein over a period of five minutes, and serial blood samples were obtained at 15, 30, 45, 60, 90, 120 and 180 minutes after the beginning of the infusion. Serum was preserved frozen at —16° C. All samples were analyzed for glucose using a glucose oxidase method (Glucose Reagent, Clinton Laboratories).

When serial concentrations of serum glucose were plotted on semilogarithmic paper, the decrease was linear between fifteen and sixty minutes. Such a method of presentation allows an interpretation of a continuing change—an advantage in detecting subtle differences. From the linear portion of the curve, rate constants of glucose clearance were calculated by the method of Lundbaek[14] and expressed as a value, k. The mean k value of 2.8 per cent per minute obtained in our patients prior to infection was well within his normal range.[14]

Serial serum samples were analyzed in triplicate for insulin by means of the double antibody radioimmunoassay of Hales and Randle.[15] Pork insulin-I-125 and precipitated antibody were obtained from Nuclear Chicago Corporation. All samples from a single tolerance test were run simultaneously. During the immunoassay, a standard curve was included with each series of patient sera. These standard curves and serum samples used as a quality control were consistent from day to day. Since methods are not available to measure the output of pancreatic insulin directly, a modification of the technic of Perley and Kipnis[16] was employed in which the area defined by plasma insulin concentrations was used as an index of timed insulin response. This area was expressed in milliunits per milliliter times minutes. Since during acute illness serum insulin concentrations remained above normal two hours following a glucose infusion, a three-hour insulin output was used as an index of response to the intravenous glucose load. Whole blood pyruvate concentrations were determined by an enzymatic method (Sigma Chemical Company, St. Louis).

The severity of illness in each patient was estimated by means of a fever index defined as the degree hours of rectal temperature greater than 100° F.

The significance of correlation coefficients was determined by variance analysis. Other results were analyzed for statistical significance with use of Student's *t* test to estimate the probability, P.[17]

RESULTS

The semilogarithmic presentation of glucose decrease during a preinfection control period, during fever, and during convalescence is shown in figure 1 as the individual values for seven subjects following the intravenous glucose load. During fever, glucose disappearance is delayed with a resultant decrease in the slope of the curve. In convalescence, the slope becomes slightly steeper and the disappearance rates begin to increase. In figure 2 are presented the mean k values (±S.E.) of these slopes before illness, during fever, and in convalescence. Note that the k values during fever are significantly depressed when compared to the preinfection control ($p<0.05$); all disappearance rates, however, were faster than those reported in diabetic patients by Lundbaek.[14] The delay in serum glucose disappearance during infection, measured in this study by a prospective approach and mathematical analysis, supported observations first recorded a generation ago.[18] The rapidity of this change deserves emphasis, however. Since the glucose tolerance tests during fever were performed within eight to twenty-four hours of the onset of clinical illness, the above recorded findings suggest that significant alterations in glucose tolerance may occur very early during clinical illness.

Average fasting serum sugar concentrations of 83.2 mg. per 100 ml. obtained during fever were significantly higher than the values obtained in the preinfection control period, 66.7 mg. per 100 ml. ($p<0.02$). Two weeks after infection the fasting serum sugar concen-

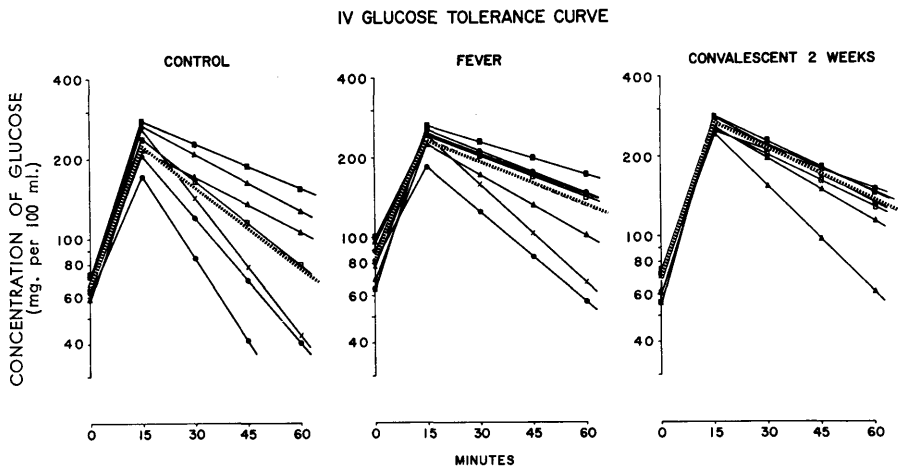

FIG. 1. Intravenous glucose tolerance curve: Serial concentrations of blood glucose in each subject have a linear relation between fifteen and sixty minutes when plotted on a semilogarithmic scale. The mean for the group is shown by a dashed line. The curves for the one afebrile subject are shown by the cross-hatched lines x-x-x-x-x.

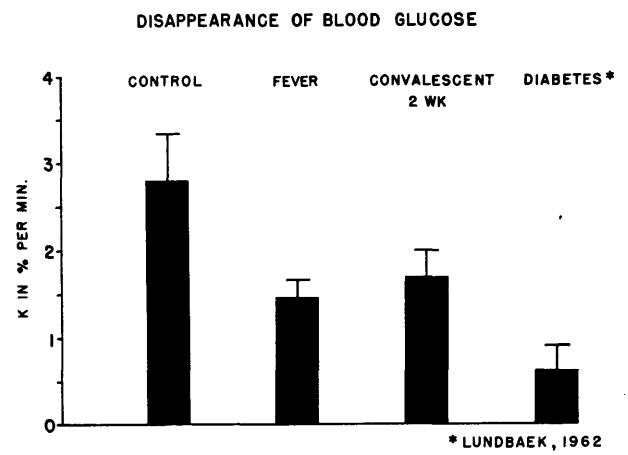

FIG. 2. Disappearance of blood glucose: Here are shown the means ± S.E. of the rate of glucose disappearance expressed as value k. The afebrile patient was excluded from the fever group. Lundbaek's data[14] to the right are depicted to include the mean and range.

trations had returned to values not significantly different from the preinfection controls.

The three-hour insulin response of each patient after the standard intravenous glucose infusion is shown in figure 3. Although sequential insulin concentrations varied between patients, the pattern of individual responses was similar. The curves during the preinfection control period showed a rapid rise of serum insulin concentration after beginning the glucose infusion. The initial average rise in concentration from 36.7 to 145.3 μU. per milliliter within thirty minutes was followed by a fall to control values by three hours. The sequential changes are comparable with the insulin response following intravenous glucose loading in normal patients described by Karam et al.[19]

During acute illness, all patients had a normal rapid onset of insulin response which reached peak concentrations within fifteen to forty-five minutes following glucose infusion; a brief plateau was present in five of the seven. Those patients with a higher fever tended to have a greater insulin response to the glucose load. The differences between control and febrile serum insulin concentrations at ninety minutes were significant ($p<0.05$); concentrations at other time periods, although higher than the control values, were not statistically different. When, however, the calculated three-hour insulin output for each febrile patient was compared to his preinfection control, the difference was significant ($p<0.02$). The one patient who remained afebrile during the clinical illness showed no change in insulin response when compared to the preinfection control.

During convalescence, insulin responses in all patients remained rapid with peak values reached by thirty minutes following the glucose infusion. Return to baseline levels occurred in two hours.

Because of the wide spectrum in clinical response, it seemed useful to compare the severity of clinical illness, glucose intolerance, and insulin response in this group of patients. To determine whether any relationship might exist between fever, the rate of serum glucose disappearance, and insulin response, these three variables were compared as shown in figure 4. To the left is shown a significant relationship between the fever index and the change in calculated insulin output.

Generally, the higher the fever, the greater the increase in insulin output. The rapidity in glucose disappearance was inversely related to the magnitude of fever, as seen to the right. In the middle are shown the rate of disappearance of serum glucose and the calculated output of insulin. Since the magnitude of in-

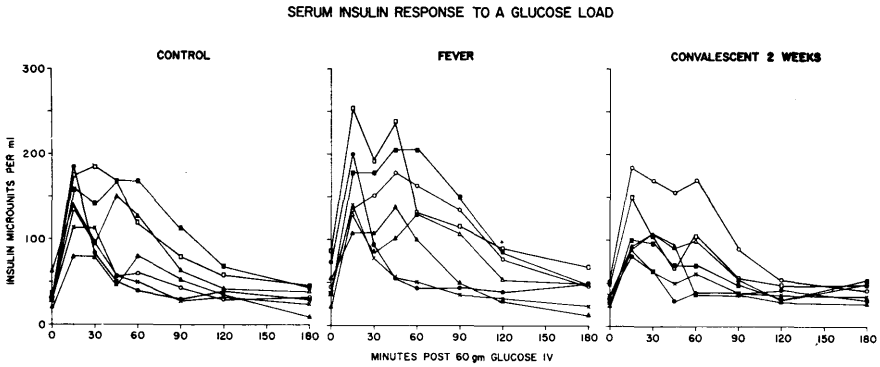

FIG. 3. Serum insulin response to a glucose load: Here are shown the serum insulin concentrations obtained serially following the glucose load. The one afebrile patient is identified by the cross-hatched lines x-x-x-x-x.

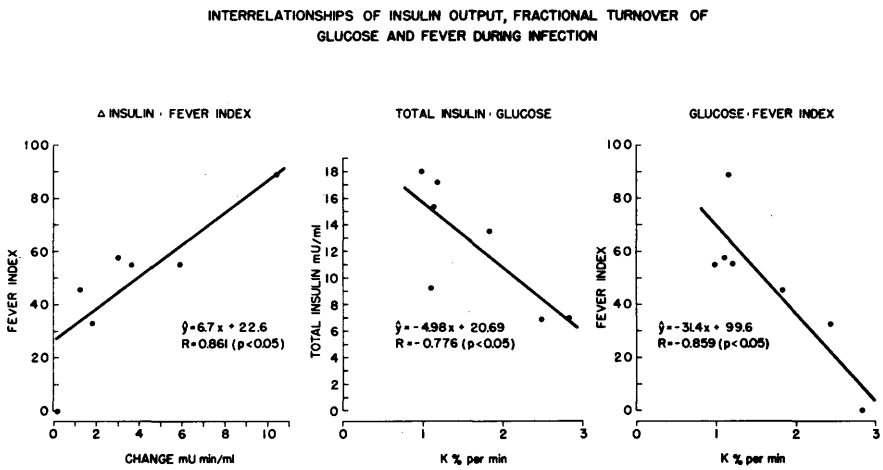

FIG. 4. Interrelationships of insulin output, fractional turnover of glucose and fever during infection: Here are presented the correlations between magnitude of fever, insulin response and rate of glucose disappearance for all seven patients. The change in insulin output compared directly with the magnitude of fever is shown to the left. In the middle is shown the inverse relationship of the three-hour insulin response to the rate of glucose disappearance. On the right is shown the inverse relationship between the magnitude of fever and the rate of glucose turnover.

sulin response was inversely related to the rapidity of the glucose disappearance, it appeared that the effectiveness of insulin was dampened. This observation is compatible with a peripheral inhibition of insulin action.

These relationships have shown that during infection in man, three events have taken place: fever, abnormalities of glucose tolerance, and an increase in insulin response to an intravenous glucose load. Although a cause and effect relationship between these events cannot be established with the data obtained from this study, the changes observed appeared to conform to a pattern in which the greatest changes tended to occur in patients with the highest fever index.

In figure 5 are depicted the insulin responses of a patient whose rectal temperature during the intravenous glucose tolerance test was 103° F. compared to those of an infected patient who was afebrile. There was a marked difference in insulin response during fever which persisted in the convalescent period after the patient had been afebrile and asymptomatic for at least ten days. The glucose tolerance tests are presented for comparison and show that the delay in serum sugar disappearance during fever persisted into the convalescent period. In the afebrile patient, the fall in serum glucose concentration was unchanged during the symptomatic period but there was a slight delay in the return to normal of serum sugar concentrations during the convalescent period.

In a second group of seven subjects infected with *P. tularensis,* the fever indices, clinical illness, and change in glucose tolerance curves were entirely similar to those of the first group when analyzed statistically. Following an identical intravenous glucose load, whole blood pyruvate concentrations were measured serially during a preinfection control period and again during fever prior to therapy, figure 6. During fever, fasting whole blood pyruvate concentrations were slightly but not significantly elevated. Following glucose infusion, pyruvate concentrations were generally higher reaching values significantly above preinfection control

at thirty and forty-five minutes ($p<.05$). Concentrations returned to fasting levels by ninety minutes in a manner similar to the preinfection control.

DISCUSSION

The present study suggests that insulin response to an intravenous glucose load is heightened during acute respiratory tularemia.

The radioimmunoassay procedure has gained wide acceptance and is contributing significantly to an understanding of the physiology of insulin secretion in a variety of conditions involving altered carbohydrate metabolism. The precision of the immunoassay between samples performed in triplicate did not vary from day to day. Hemoconcentration did not appear to contribute to increased insulin concentrations since hematocrits showed no change during illness. Even if the immunoassay procedure failed to detect biologically inactive insulin,[20] evidence for increased physiologically active insulin theoretically would remain valid. The method of calculation of a three-hour insulin response, however, is far from ideal and may not represent an accurate estimation of pancreatic insulin secretion. This approach has, however, proved useful to other investigators in the formulation of working concepts.[16,21]

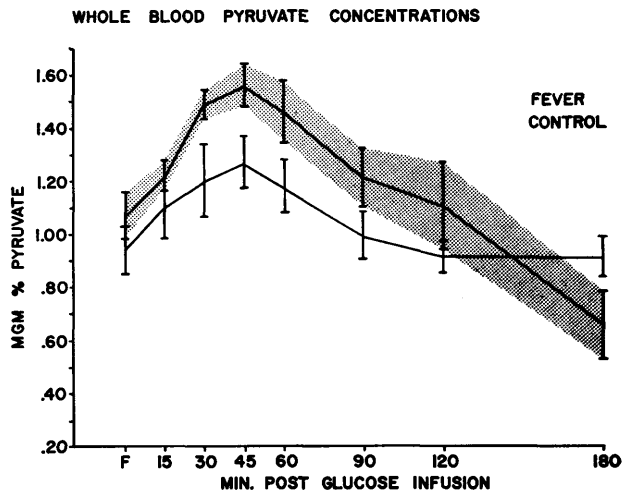

FIG. 6. Whole blood pyruvate concentrations during tularemia in man: Here are shown the mean with its standard error of whole blood pyruvate concentrations following a glucose load given to a second group of tularemia patients during a preinfection control period and during fever prior to therapy. Whole blood pyruvate concentrations during infection, shown in stippled area, were generally higher and reached significant elevations above normal ($p < .05$) at thirty and forty-five minutes following the glucose infusion.

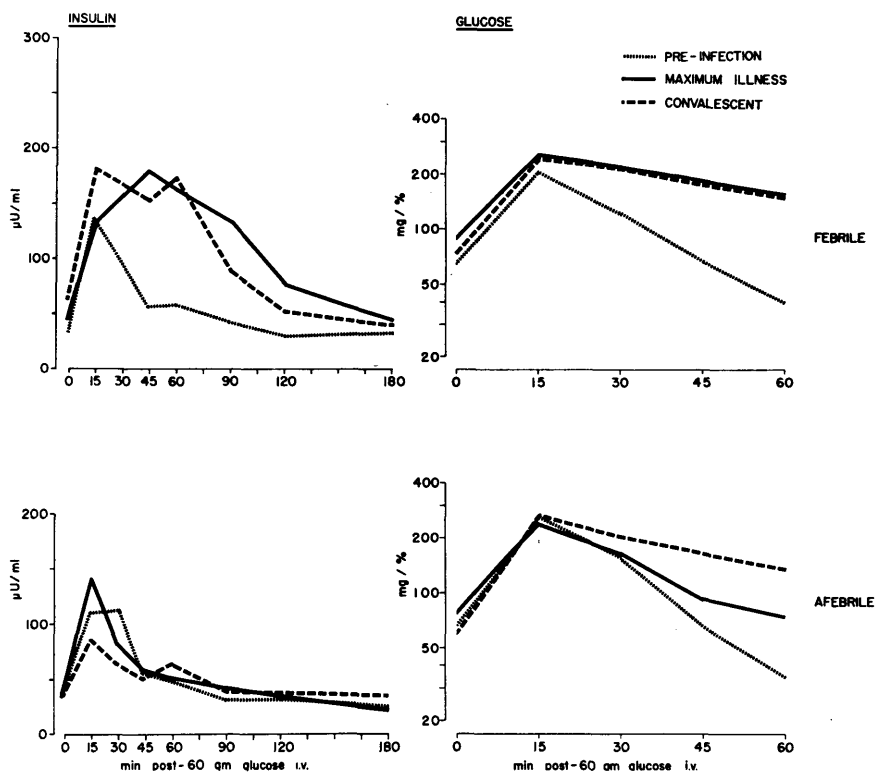

FIG. 5. The effect of fever on glucose disappearance and insulin response: Here are compared the patient with the greatest magnitude of fever and the afebrile patient. The increased insulin response and the delayed disappearance of serum glucose concentrations seen in the febrile patient persist into convalescence twelve days following return of the temperature to normal. The afebrile patient had no change in the pattern of insulin response, but the disappearance of serum glucose concentrations was slightly delayed during convalescence.

Since a large number of metabolic changes in acute tularemia resemble those seen in other infectious diseases studied in this laboratory, it is reasonable to postulate that similar changes in insulin response may occur in a variety of infections.

The clinical spectrum of illness in these patients afforded an opportunity to measure insulin response during varying degrees of illness. The data suggest that the insulin response to a glucose load may be related in part to the severity of illness as measured by fever, but is not dependent on the presence of fever. As noted above, however, the fever index of individual subjects did correlate positively with the magnitude of increase in the insulin response. It must be recalled that all patients were studied during the first day of clinical illness. The magnitude of insulin response reported herein may not, therefore, be representative of conditions which may evolve during a prolonged or severe infection.

Various factors which change carbohydrate metabolism produce unique patterns of insulin response to a glucose load. In the maturity onset diabetic patients, the onset of insulin response to intravenous glucose load may be delayed, the rise is slow, and peak concentrations are markedly elevated.[22] The fall in insulin concentrations is also delayed.[23] The patterns after oral glucose loading in early maturity onset diabetic patients are similar.[24] In obese nondiabetic subjects with a normal disappearance of infused glucose there is an initial rapid insulin response with serum insulin concentrations that remain on a plateau at values considerably higher than normal for more than one hour.[19] Only a limited number of studies after oral glucose loading have been performed in normal subjects following glucocorticoid administration.[16,21] In these subjects there was a normal rapid onset of insulin response, but the peak concentrations were higher. Acromegalics may show a similar pattern.[19]

The insulin response observed during infection showed a normal rapid onset with a tendency to form a brief plateau close to peak values. Both peak values and calculated three-hour response were generally higher than the control. Since the fall in insulin concentration was slightly delayed, serum concentrations at ninety minutes were still in excess of normal values at that time. This pattern of response is not typical of that seen in maturity onset diabetes which has a delayed onset. The insulin response curve in obese subjects tends to show a more prolonged plateau but has a rapid initial rise.[19]

Elevated whole blood pyruvate concentrations seen in the second tularemia group following glucose loading resembles the elevation reported following administration of adrenal steroids.[25] Such an exaggerated rise in blood pyruvate following a glucose load is not seen in obesity.[26,27] It is possible that changes in patterns seen during infectious illness were due, in part, to glucocorticoid excess. In patients with tularemia of similar severity to those reported in this study, maximum urinary 17-hydroxycorticosteroid excretion at the height of fever approached twice baseline; this output of 17-hydroxycorticosteroids in typical tularemia was reproduced in a control study in normal subjects by orally administered cortisol, with a maximum dose of 72 mg. per day.[28] Berger et al.[21] used a comparable dose during their cortisone-modified glucose tolerance studies in which serum insulin responses were calculated. The dose of dexamethasone used by Perley and Kipnis[16] to alter the insulin response was severalfold greater in potency.

An elevated blood glucose has been shown to enhance insulin output in man.[29] The mechanism involved appears to be stimulation of beta cell release.[30] Although such a mechanism might be altered during fever, our one afebrile patient had a delay in the return of serum glucose concentrations to normal with no significant change in the insulin response. A role of glucagon in the enhanced stimulation of insulin secretion during infection has yet to be investigated.[31-33]

Other factors, singly, or in combination, may play a role. The increased concentrations of serum insulin during fever bore an inverse relationship to the rate of glucose disappearance after the intravenous load, an observation compatible with peripheral inhibition of insulin action. Known mechanisms of insulin inhibition that might be considered include an increased destruction of insulin,[34] factors interfering with the peripheral action of insulin such as elevated concentrations of nonesterified fatty acids,[9,35,36] alteration of enzyme systems which regulate carbohydrate metabolism[6,7,10,37]; and a possible increase in growth hormone secretion. Growth hormone which enhanced insulin output following glucose loading in patients with hypopituitarism[8] as well as in acromegaly,[38,39] has also been shown in dogs to inhibit pyruvate metabolism.[40]

A diminished sensitivity to insulin during infection may have its counterpart in other stress-producing situations. Howard[41] noted an insulin insensitivity in trauma patients that appeared to be directly related to the severity of the trauma. The abnormality in glucose

tolerance and the heightened insulin response to a glucose load during infection appeared to be directly related to the magnitude of fever and may represent a pattern of stress response.

Although a modest increase in glucocorticoid output with a superimposed elevation of blood sugar might explain the enhanced insulin response during acute illness, other factors may continue to be operative during convalescence. Understanding the pathogenesis of these alterations, however, awaits further investigation.

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Reports of the Committee on Nutrition, American Academy of Pediatrics

For several years the Committee on Nutrition of the American Academy of Pediatrics has been considering a number of nutritional matters of importance in the care of infants and children. A number of articles in *Pediatrics* have resulted from the activities of this committee, one of whose aims is to provide up-to-date information on various nutritional topics for the practicing pediatrician.

Three such reviews were published recently. The first is a short review of vitamin E in human nutrition (Pediatrics *31*:324, 1963). Work concerned with attempts to induce vitamin E deficiency in adult humans, the differences in serum tocopherol levels in infants fed cows' milk and human milk, and the presumptive evidence of vitamin E deficiency in children with steatorrhea are discussed. The matter of susceptibility of erythrocytes to oxidative hemolysis in subjects with low levels of serum tocopherol is taken up, with the conclusion that "premature and full term infants receiving human milk or formulas of cow milk do not require supplementary administration of vitamin E except, possibly, when dietary intake of fat is markedly reduced, as is sometimes practiced in feeding premature infants. It seems desirable to provide dietary supplements of vitamin E to patients with prolonged steatorrhea from any cause."

The second review is an appraisal of nutritional adequacy of infant formulas used as cow milk substitutes (Pediatrics *31*:329, 1963). The importance of this subject derives from the fact that an increasing number of infants in the U.S.A. are being given diets devoid of cows' milk because of allergic reactions. Milk has always been the principal ingredient of the infant diet, and the committee felt that data concerning the composition of the various milk free diets available on the market should be made available to the pediatrician. The composition of soya milks, meat base formulas, goat milk, and formulas based on protein hydrolysate is given. Attention is directed to the variations encountered in commercial preparations, particularly in regard to vitamin content. Some new data on protein efficiency ratios for soya milk and meat base formulas are presented.

The third review concerns the prophylactic requirement and the toxicity of vitamin D (Pediatrics *31*:512, 1963). Existing data on the requirement of the vitamin in infants, children, and adults are reviewed. It is apparent from this that the NRC recommended allowance of 400 units daily provides an ample margin of safety. Attention is given to the toxicity of this vitamin, and to its presumed causative role in the infantile hypercalcemic syndrome.

One of the more interesting aspects of the report has to do with the fortification with vitamin D of foods other than milk. The addition of vitamin D to milk flavorings, and to some brands of margarine and cereals, is such as to raise the total intake of many children to a value equal to or in excess of the recommended allowance, in the absence of specified vitamin supplements.

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