(during its effective period) upon glycosuria and hyperglycemia produced by ACTH.[4]

The effect of GSH in simultaneously reversing ACTH-induced hyperglycemia and renal glycosuria seems all the more striking since sudden cessation of glycosuria would be expected to result in further increase of hyperglycemia were the rate of utilization of glucose not significantly increased or the supply to the blood significantly decreased. Since a severe degree of negative nitrogen balance remained uninfluenced by GSH, decreased glyconeogenesis from protein was probably not a factor. That hepatic glycogenolysis may have been inhibited remains as a possibility to explain the fall of blood sugar.

Since GSH inactivates insulin *in vitro*, such an effect *in vivo* should have raised the blood sugar level. If this occurred to any degree, its effect was minor as compared with those forces which produced an actual fall of circulating blood sugar.

Also observed were other metabolic reversals of major significance. Among the most striking was a profound change in the number and character of the circulating white blood cells. This remarkable change, which lasted 1–2 hrs, was opposite in direction to the effects which we have observed repeatedly in normal people receiving ACTH for a number of days (*4*). These findings are being reported in detail elsewhere.

Not all of the metabolic effects of increased adrenal corticoid activity were reversed by administration of GSH. This indicates that reversal of those metabolic effects which responded to GSH was not by virtue of a block in steroid production. It seems likely that the changes are due to improved performance of those systems which require free sulfhydryl groups for their normal function. This appears to be the case with respect to (1) renal tubular reabsorption of glucose, (2) the systems involved in utilization of glucose, and (3) the systems responsible for production and release of white blood cells.

It is believed that the results reported give added weight to our hypothesis. The forces at work in the early stages of the development of human diabetes may be very similar to those described in this and in our previous studies. Of somewhat broader significance are the implications with respect to abnormalities of metabolism generally. Hormonal control of enzymatic processes, mediated via independent effects of the same hormone upon other systems, appears to be a fertile field for future investigations. But it implies the necessity of establishing technics which can be applied in the intact animal or man.

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Production of Acute Gouty Arthritis by Adrenocorticotropin[1]

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It has long been known that attacks of acute gouty arthritis can be precipitated by exposure to nonspecific stresses such as trauma, infection, operation, chilling, foreign protein therapy, X-radiation, and many other stimuli. These stresses have been shown to produce a syndrome of increased adrenal cortical activity (*5*) and associated biochemical and histologic changes, commonly referred to as "the alarm reaction" (*4*).

It is likely that all forms of nonspecific stress call forth increased adrenal cortical activity through a common pathway. This pathway is increased secretion of pituitary adrenocorticotropin (ACTH), which in turn stimulates the adrenal cortex (*4*).

ACTH has therefore been given to four patients with gout and has precipitated three attacks of acute gouty arthritis in five trials. The entire syndrome of electrolyte and water changes observed to occur with the acute attack of gout (*7*) has also been reproduced by the administration of ACTH.

In addition, since it was shown that the attack of gout follows a phase of relatively decreased adrenal cortical activity, the administration of ACTH to two patients during an attack of acute gouty arthritis produced a prompt disappearance of the acute arthritis. This aspect of the action of ACTH resembles that of colchicine, which relieves the acute attack of gout and is a potent stimulus to increased adrenal activity (*2*).

Three of the four patients were studied on a metabolic ward and received diets of known composition. After a contral period of four days, 150 mg (equivalent to Armour standard) ACTH[3] was given by intramuscular injection each day in divided doses for four days.

Control serum uric acid was elevated in all patients. During the administration of ACTH, there was an increase in urinary uric acid and nitrogen and a decrease in sodium and chloride excretion. Three patients had glycosuria of one to three gm daily. In two patients, there was a significant increase in glomerular filtration rate, renal plasma flow, and uric acid clearance (*1*). The circulating eosinophils disappeared while ACTH was being given.

For three days following completion of the ACTH injections, there was an excretion of sodium and chloride considerably greater than the control values while the uric acid excretion returned to the control value. The

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increased electrolyte excretions may be interpreted as a phase of decreased adrenal cortical activity due to withdrawal of the ACTH.

The attacks of acute gouty arthritis began during the third and fourth days of the postinjection period, when the electrolyte and water diuresis was almost completed. Each attack resembled the classic picture of acute monoarticular arthritis. The two patients who did not develop acute arthritis nevertheless exhibited similar changes in urinary excretion during and following the administration of ACTH. This sequence of electrolyte changes in gouty patients has previously been described as "the gout cycle" (*6*).

In two attacks, one of which had been provoked by ACTH and the other by a mercurial diuretic, 200 mg ACTH given over a 36-hour period starting on the first day of the attack was followed by a disappearance of joint signs within 48 hours after the injections were completed. Untreated attacks of acute arthritis in these patients had previously lasted 10 to 14 days. The increased electrolyte excretion following the mercurial diuretic mimics "the gout cycle" and in this manner may be involved in precipitating the attack of acute arthritis.

The results suggest that stimulation of adrenal cortical function is the common pathway in the precipitation of acute gouty arthritis by nonspecific stress and that pituitary adrenocorticotropin may be useful as a provocative and therapeutic agent in gout.

Since this work was completed, similar results have been reported in one patient (*3*).

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A Simple Method for Welding Thermocouples

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The use of thermocouples in physiological problems, for such purposes as recording respiration or blood flow, necessitates the use of very small wires which often are very difficult to solder or braze by conventional methods. Furthermore, the sensitivity of the thermocouple is dependent on the type of joint, for a large juncture allows local currents of considerable magnitude to flow, thus reducing the effective voltage output. The introduction of foreign metals in the soldering or brazing process sets up contact electromotive forces with the same deleterious effects.

These metals may be welded, however, by the method to be presented here. The materials necessary are shown in Fig. 1. It is simply a metal cup containing a few

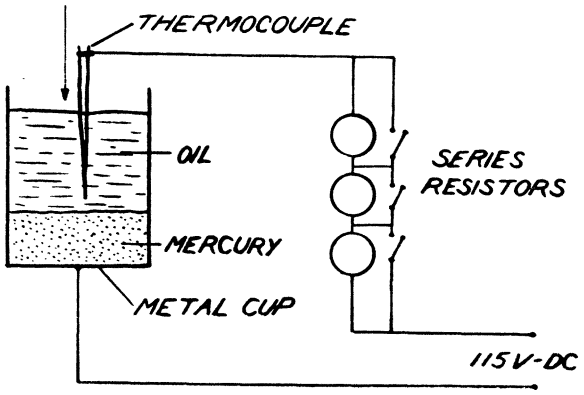

FIG-1

millimeters of mercury under about 2–3 cm of oil. Mineral oil or 10–30W motor oil may be used. In the apparatus now in use in this laboratory, the cup consists of the inverted metal shell of a vacuum tube with a grid cap (6J7). The cup is connected to one side of the d-c main, and the thermocouple wires to the other side through a series resistor as shown. The thermocouple is then moved down to touch the surface of the mercury and withdrawn. Welding is accomplished by heat from the arc formed at the moment of contact with the mercury. A "buzz" accompanied by slight boiling in the oil layer signifies good contact. The size of the series resistor depends on the size of the wires to be welded, as a larger current will be required for larger wires. We use a 400-w heating element for 0.3-mm iron-constantan couples. A little experimentation will quickly show the optimum value of current, as too much current causes burning of the wires with a large junction, and too little current does not weld at all.

The method of preparing the wires for welding is as follows: They are first twisted tightly together for a distance of several millimeters; the distal end of the twisted junction is then cut off so that only a turn or so remains. The wires are now ready to weld, and after welding they may be untwisted if any of the twisted portion remains unfused, so that the wires are joined only by a small ball of fused metal. This ball should be as small as possible, without sacrificing the strength of the joint.

This method has been utilized with iron-constantan, platinum-platinum-rhodium, chromel-alumel, and copper-constantan couples, with wire sizes from 0.1 mm to 4 mm. A larger cup with more and heavier oil is required for the larger wires. The circuit should be fused in all cases.