2. Thyroxin wirkt als Antagonist hemmend auf die Fettbildung, die durch Cortison beim hypophysektomierten Pavian angeregt wird.

3. Starke Leberverfettung entsteht bei hypophysektomierten Pavianen nach gleichzeitiger Entziehung von Cortison und Thyroxin.

## Effect of Hormonal and Dietary Treatments on Lipogenesis from Acetate in Hereditarily Obese Hyperglycemic Mice[1]

In a series of publications (e.g. BATES, MAYER, and NAUSS[2]; BATES, ZOMZELY, and MAYER[3]; MAYER and ZIGHERA[4]) it has been shown that mice with the hereditary obese hyperglycemic syndrome were characterized by an increased rate of acetate incorporation into fatty acids over their non obese litter mates, even under conditions of paired feeding, restricted feeding or fasting. Under such conditions, goldthioglucose obese mice, hypothalamic hyperphagic rats and hypothalamic mice do not exhibit such an increase. Under conditions of *ad libitum* intake lipogenesis from acetate in obese mice can reach four times the normal value.

A possible explanation of the mechanism of development of the hereditary obese hyperglycemic syndrome has been offered (MAYER, ANDRUS, and SILIDES[5]). It was suggested that these animals were characterized by hypersecretion of a pancreatic hyperglycemic hormone, presumably glucagon and a secondary hypersecretion of insulin. It was further suggested that growth hormone may be trophic to the hyperglycemic factor. It has since been demonstrated (WRENSHALL, ANDRUS and MAYER[6]) that mice with the syndrome did in fact show hyperplasia of the islets of Langerhans, and an increased pancreatic insulin content, in spite of degranulation of cells, consistent with a picture of hypersecretion. As for the possibility of increased glucagon secretion, it has been shown that the mice show a considerably increased rate of glycogen turnover (SHULL and MAYER[7]), corresponding increased liver phosphorylase activity (SHULL, ASHMORE, and MAYER[8]) and a sixfold increase in pancreatic glucagon content after treatment with growth hormone (CLARKE, WRENSHALL, and MAYER[9], to be submitted). Normal mice do not show this increase. Growth hormone induces hyperglycemia in obese mice (MAYER and SILIDES[10]; SHULL and MAYER[7]) and obese mice are particularly sensitive to glucagon (SHULL and MAYER[7]). In view of these considerations, it appeared of particular interest to see how insulin, insulin combined with hyperglycemia, growth hormone and glucagon affected acetate incorporation in mice with the obese hyperglycemic syndrome and their controls. Because these obese mice on a high fat diet, unlike goldthioglucose (MARSHALL and MAYER[11]) and hypothalamic (MAYER *et al.*[12]) obese mice, are considerably slowed down in their rate of weight gain (MAYER and JONES[13]), it appeared worthwhile to compare effects of this diet on the acetate incorporation into fatty acids in obese and non obese animals.

*Methods.* The animals used were hereditarily obese hyperglycemic mice, and their non obese litter mates, 4 to 6 months of age. The weight of the obese mice were in the 40 to 60 g range, that of the non obese 20 to 30 g. All animals were housed in individual cages for at least 3 days prior to the experiment. Unless otherwise noted they were fed Purina Laboratory chow *ad libitum*. Fasted animals were subjected to an 18 h fast. The animals on the high fat diet were fed for the 10 days preceeding the experiment the carbohydrate free diet previously described (MAYER and JONES[13]). The $C^{14}$ carboxyl labeled acetate was given intraperitoneally in 0·5 $cm^3$ water solution in measured doses of approximately $10^6$ c.p.m. in the case of the obese animals and $10^6$ c.p.m. in the case of the non obese. Hormones and glucose were given intraperitoneally in 0·25 $cm^3$ solution. Doses are given in the Table. In the case of the studies using insulin, insulin alone, or insulin with glucose, these injections were given 15 min before labeled acetate administration. In the experiment in which both insulin and glucose were given blood glucose determinations showed that the non obese animals were hyperglycemic (levels of 200 mg % or more) for at least 20 min following injections. The blood glucose levels were back at pretreatment levels after 30 min. Control saline injections had no such effect. Glucagon was injected 10 min before acetate was given. The animals were sacrificed 30 min after acetate administration. The procedure used to determine counts retained in liver and carcass (defined as body *minus* liver) fatty acids has been described in detail previously (BATES, MAYER, NAUSS[3]; BATES, ZOMZELY, MAYER[4]). The significance and limitations of the method have been discussed in a recent paper (BATES, ZOMZELY and MAYER).

*Results and discussion.* The results, expressed in percent counts retained multiplied by $10^3$, are given in the Table. Significance of the differences with the untreated animals, calculated by Student's "t" method, are included. It is readily seen that insulin considerably increases lipogenesis from acetate both in non obese and in obese animals. The fact that the level reached in the carcass of the obese animals is hardly higher than that reached by the non obese animals may indicate that the upper limit is set by factors other than circulating insulin or that, alternately, the dose of insulin given is very large in comparison to the amount of circulating insulin. Liver synthesis was increased proportionately less than peripherial synthesis. The effect of growth hormone, studied at two time intervals because of the observed delay in the hyperglycemic action in obese mice (SHULL and MAYER[7]), shows that growth hormone

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Acetate incorporation into fatty acids following hormone and dietary treatment.

| Treatment | Obese animals | | Non obese animals | | Total retention | |
|---|---|---|---|---|---|---|
| | Carcass | Liver | Carcass | Liver | Obese | Non obese |
| Controls: ¼ cm³ Saline | 1088 ± 245<br>26 animals | 892 ± 194<br>25 animals | 324 ± 113<br>14 animals | 181 ± 118<br>14 animals | 1980 ± 318<br>26 animals | 505 ± 197<br>14 animals |
| Insulin · 3 IU/mouse | 2146 ± 189$^{++}$<br>6 animals | 986 ± 202<br>6 animals | 2102 ± 395$^{++}$<br>6 animals | 498 ± 150$^{++}$<br>6 animals | 3132 ± 166$^{++}$<br>6 animals | 2600 ± 500$^{++}$<br>6 animals |
| Insulin · 3 IU/mouse + glucose 100 mg/mouse | 1622 ± 390$^{++}$<br>10 animals | 1251 ± 360$^{++}$<br>10 animals | 1999 ± 268$^{++}$<br>10 animals | 283 ± 74$^{+}$<br>10 animals | 2873 ± 472$^{++}$<br>10 animals | 2282 ± 224$^{++}$<br>10 animals |
| Growth Hormone 2 mg/mouse 3 h after | 680 ± 115$^{++}$<br>6 animals | 549 ± 244$^{++}$<br>6 animals | 1043 ± 231$^{++}$<br>6 animals | 252 ± 67<br>6 animals | 1229 ± 345$^{++}$<br>6 animals | 1295 ± 276$^{++}$<br>6 animals |
| Growth Hormone 2 mg/mouse 12 h after | 987 ± 248<br>10 animals | 862 ± 267<br>10 animals | 472 ± 174$^{++}$<br>10 animals | 210 ± 101<br>10 animals | 1849 ± 263<br>10 animals | 682 ± 261<br>10 animals |
| H.G.F. 100 µg/mouse | 841 ± 188$^{++}$<br>10 animals | 495 ± 85$^{++}$<br>10 animals | 1127 ± 259$^{++}$<br>10 animals | 116 ± 52$^{++}$<br>10 animals | 1336 ± 233$^{++}$<br>10 animals | 1243 ± 329$^{++}$<br>10 animals |
| Fasting | 353 ± 70$^{++}$<br>6 animals | 26 ± 6$^{++}$<br>6 animals | 208 ± 59$^{+}$<br>6 animals | 7 ± 3$^{++}$<br>6 animals | 379 ± 63$^{++}$<br>6 animals | 215 ± 41$^{++}$<br>6 animals |
| Fasting + 100 µg/mouse H.G.F. | — | — | 503 ± 217$^{++}$<br>6 animals | 46 ± 33$^{+}$<br>6 animals | — | 549 ± 242<br>6 animals |
| High Fat Diet | 572 ± 166$^{++}$<br>6 animals | 21 ± 13$^{++}$<br>6 animals | 225 ± 76<br>6 animals | 12 ± 5$^{++}$<br>6 animals | 593 ± 174$^{++}$<br>6 animals | 237 ± 72$^{++}$<br>6 animals |

1. All data are expressed as percent counts × $10^3$.
2. Figures following ± are standard deviations.
3. Significance of differences with untreated values calculated by Student's method: $^{+}p < 0.05$, $^{++}p < 0.01$.

administration has opposite actions as regards acetate incorporation in obese and in non obese animals. It decreases lipogenesis from acetate in the obese mice, at least at the 3 h interval, but it increases lipogenesis from acetate very significantly in the non obese animals. This finding may give an interpretation to the fact that growth hormone has a hyperglycemic action in the obese animals and not in the non obese animals. The effect of glucagon on both the obese and the non obese animals is similar to that of growth hormone: decreased lipogenesis from acetate in obese animals, increased lipogenesis in the non obese. Again these findings may give an interpretation of the differential effects of glucagon on blood sugar. The similarity between the effects of growth hormone and glucagon in this respect may also be construed to indicate that part of the action of growth hormone may be mediated through increased glucagon secretion. This suggestion is supported by previous evidence on the effect of diethyldithiocarbamate (DEDTC) administration (MAYER, ANDRUS, and SILIDES)[5] and increased pancreatic glucagon in the obese animals following growth hormone administration. This concept is also in accord with the results of BORNSTEIN, REID, and YOUNG[14] and FOA *et al.*[15]. On the other hand the fact that glucagon, but not growth hormone, causes an increase in the blood sugar level of fasted obese mice is still unexplained. It could be due to concentration or to a delay of action effect. Fasting as previously shown considerably decreases lipogenesis from acetate in obese as well as in non obese animals. As has been shown to be characteristic of "metabolic obesity" the rate of lipogenesis is still significantly higher ($p < 0.01$) in fasted obese than in fasted non obese mice. When glucagon is given to fasted non obese mice the resultant lipogenesis picture is very similar to that obtained in untreated fasted obese mice, a finding of particular interest in view of the suggested etiology. Finally, placing the animals on a high fat diet depresses lipogenesis from acetate both in the obese and in the non obese animals. In view of the considerable slow down in weight gain shown by obese hyperglycemic mice on this diet it is of interest to note that the decrease in lipogenesis, is both proportionately and absolutely, much greater in obese than in non obese mice.

D. J. SILIDES and J. MAYER

*Department of Nutrition, Harvard University, School of Public Health, Boston, October 27, 1955.*

*Zusammenfassung*

Es wird die Wirkung einer Behandlung mit verschiedenen Hormonen und Kostformen auf den Azetateinbau in Fettsäuren bei erblich fettsüchtigen Mäusen und ihren normalen Geschwistern aus dem gleichen Wurf untersucht. Insulin, mit und ohne Glukose verabreicht, steigert die Lipogenese bei beiden Mäusetypen. Wachstumshormon und Glukagon vermindern den Azetateinbau bei den fettsüchtigen, vermehren ihn aber bei nichtfetten Tieren. Glukagon bewirkt bei normalen Tieren eine Steigerung der Einbaurate, die der bei unbehandelten fettsüchtigen gleichkommt. Fütterung einer fettreichen Kost senkt die Lipogenese bei fettsüchtigen Mäusen in stärkerem Ausmass als bei nichtfettsüchtigen.

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