SECTION 3
STUDIES ON THE ROLE OF THE ADRENERGIC SYSTEM
IN THE THERMOLYCEMIC RESPONSE

CHAPTER I
STUDIES ON THE ROLE OF THE ADRENERGIC SYSTEM
WITH GANGLIOLYPTIC AND ADRENERGIC BLOCKING AGENTS
Introduction

Claude Bernard (1855) first demonstrated that lesions in the floor of the fourth ventricle of the brain may produce hyperglycemia. By section of the splanchnic nerves this hyperglycemic response can be prevented, although this is not due entirely to inactivation of the adrenal medulla since such hyperglycemia may also occur in demedullated animals. During adaptive responses simultaneous activation of the nervous system may account in part for some of the metabolic changes observed.

Activation of the sympathetic-adrenal medullary system has been shown to occur in almost all known types of stresses. Such sympathetic hyperactivity was deduced from responses in the experimental animal itself (Heymans, 1929). Stresses such as cold (Morin, 1946; Cannon et al., 1927), heat (Cannon et al., 1927a), hemorrhage (Filcher and Sollman, 1914; Tournade and Chabrol, 1925), fear (Cannon and Britton, 1925, 1927), burns (Hartman et al., 1926), pain (Cannon, 1919), fever (Von Euler, 1929), infections (Cannon and Paraíra, 1924), dehydration (Freeman et al., 1933) and others were shown to evoke sympathetic and medullary activity. An "emergency" role for the sympathetic medullary system was formulated by Cannon and it has received much additional support (Gelander, 1954). Cannon et al. (1927) demonstrated that the sympathetic system is not essential to life in the relatively stable environment of the laboratory. However, it is recognized that in the varied environment of ordinary life situations sympathectomized animals do not function adequately (Cannon et al., 1929). The range of adaptive responses is narrowed both in adrenalectomy and sympathectomy and it is reported that adrenalectomy produces a much greater stress sensitivity (Anderson, 1943). Indeed, it was from a
consideration of sympathetic responses to environmental stresses that Cannon and his co-workers developed the concept of the maintenance of a balance of vital parameters in the face of internal and external changes; a concept embraced in Cannon's term "homeostasis" (Cannon, 1939).

Sympathectomized animals, in general, show inadequate responses to stress concerning maintenance of blood pressure, blood sugar, body temperature, etc., as well as a prolonged recovery time. Subjected to the same degree of stress the adrenalectomized animal does not recover (Hartman and Winter, 1933). It has been reported that a marked impairment in carbohydrate metabolism, exhibiting hypoglycemia on exerting and marked insulin sensitivity is seen in adrenalectomized animals (Sayers, 1950; Britton, 1950; Noble, 1955).

Epinephrine has been shown to activate the enzyme phosphorylase, prompting in vivo the in vitro synthesis and breakdown of glycogen (Sutherland, 1951). Recent data appear to favor the concept that epinephrine inhibits glucose uptake by muscle. It has been demonstrated by Walaas and others (Walaas, 1955; Sutherland, 1952; Walaas and Walaas, 1960) that epinephrine in a physiological dose range, exerts an inhibitory effect on glucose uptake by diaphragms. With consideration of these facts the role of the adrenergic system in the thermoglycemic response has been studied in this chapter with ganglioplegic and adrenergic blocking agents.

Experimental Methods

Healthy pigeons weighing to 275 g. and baby rabbits weighing to 295 g. were used. All the animals were fasted for 14 hours before the experiments were conducted. Fifty-four pigeons and fifty-four rabbits were housed in individual cages in a room with an average ambient temperature of 32°C. In series I thirty pigeons were divided into two groups and after
collecting a sample of wing vein blood for sugar estimation, a ganglion-blocking agent, Ansolysen brand pentolinium tartarate (M & B 2050 A), which is chemically pentamethylene 1,6-bis (1-methyl pyrrolidinium) hydrogen tartrate was injected intramuscularly into the birds of both groups. One group was then kept as a control at 32°C and the other subjected to 48°C for 2½ hours under similar conditions as described in Parts I and II.

Thirty baby rabbits were similarly grouped and after collecting a sample of ear vein blood for sugar estimation Ansolysen was injected intramuscularly into the animals of both groups. One group was similarly kept as a control at 32°C and the other subjected to 48°C for 2½ hours under identical conditions. The optimum dose of Ansolysen at which complete blockade of the ganglion occurs was determined previously in rabbits and pigeons from the effect on the electro-cardiogram to a known tachycardic response of epinephrine. Both in rabbits and pigeons 0.4 mg./kg. body weight Ansolysen injected intramuscularly was found to be sufficient for the complete block of the ganglia for more than 90 minutes. A second similar dose after this period could maintain the block for another 90 minutes. The blocking effect in the exposed rabbits and pigeons was therefore maintained by a second dose of Ansolysen 90 minutes from the time of exposure. After a period of exposure for 2½ hours blood samples were taken for sugar estimation.

In series 2, twenty-four pigeons were divided into two groups. After collecting a blood sample for sugar estimation, an adrenergic blocking agent, ergotamine tartrate 25 µg./kg. body weight was injected intramuscularly. One group was kept control at 32°C and the other subjected to an ambient temperature of 48°C for 2½ hours. Twenty-four baby rabbits were similarly divided into two groups and after collecting a sample of
Table 1

Effect of exposure of pigeons and baby rabbits controlled at 32°C to high ambient temperatures of 48°C and 45°C respectively for a period of 2½ hours on the blood sugar level in mg./100 ml. with treatment by the ganglioplegic drug Ansolsen and the adrenergic blocking agent ergotamine tartrate.

<table>
<thead>
<tr>
<th>Ambient temperature</th>
<th>32°C</th>
<th>45°C</th>
<th>46°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansolsen (pigeon)</td>
<td>119.8±10.1</td>
<td>120.8±11.0</td>
<td></td>
</tr>
<tr>
<td>Ergotamine tartrate (pigeon)</td>
<td>118.3±10.4</td>
<td>117.4±9.96</td>
<td></td>
</tr>
<tr>
<td>Ansolsen (rabbit)</td>
<td>67.7±5.2</td>
<td>69.2±6.1</td>
<td></td>
</tr>
<tr>
<td>Ergotamine tartrate (rabbit)</td>
<td>66.2±5.3</td>
<td>67.2±5.3</td>
<td></td>
</tr>
</tbody>
</table>
blood for sugar estimation ergotamine tartrate 50 μg/kg. body weight was injected intramuscularly. One group was similarly kept control at 32°C and the other exposed to 45°C for 2½ hours. After the period of exposure was over blood samples were collected from all the rabbits and pigeons and sugar determined.

**Results**

Ansolysen brand pentolinium tartrate is chemically pentamethylene-1,5-bis (1-methylpyrrolidinium) hydrogen tartrate and it can be represented by the following structural formula:

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{N}^+ & \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_2 & \text{CH}_3
\end{align*}
\]

2C₄H₅O₆

ANSOLYSEN
Fig. 1. Effect of exposure of pigeons controlled at 32°C to high ambient temperature of 48°C for a period of 2½ hours on the blood sugar level in mg./100 ml. with treatment by the ganglioplegic drug Ansolysen, 0.4 mg./kg. body weight.
Fig. 2. Blood sugar levels of pigeons housed at 32°C and exposed to high ambient temperature of 48°C for 2½ hours with treatment by the adrenergic blocking agent Ergotamine Tartrate, 25 µg/kg. body weight.
The pharmacology of Ansolyses has been studied and reported by Wien and Mason (1953) and Mason and Wien (1955). Its primary activity is inhibition of nervous transmission between the pre- and post-ganglionic neurones of the autonomic nervous system.

Administration of "Ansolyses" per se at 32°C had no effect on the blood sugar level of the rabbits and pigeons and exposure to 46°C and 48°C of the rabbits and pigeons respectively caused no increase blood sugar level in these animals. When hyperglycemia was induced, it is caused by an increased consumption of glucose. Since this greater mobilization of sugar occurs through the adrenergic system, ergotamine and other ergot alkaloids show that after blocking the adrenergic response in rabbit, an appreciable decrease in tachycardia was recorded after these blocking agents.

The results are shown in Table 1. The results have also been represented graphically in Figs. 1, 2, 3 and 4.

Discussion

A majority of the available adrenergic blocking agents diminish or block many of the excitatory effects of epinephrine. As early as 1912, Mienlieich demonstrated that ergotoxine reduced the rise in blood sugar induced by epinephrine in the rabbit. Rothlin (1946), Harvey et al (1950), Ellis and Anderson (1950) and Konrad and Low (1951) showed that the ergot alkaloids are quite active in preventing epinephrine induced hyperglycemia. Rothlin (1946) reported that the dehydrogenated and naturally occurring ergot alkaloids are capable of preventing the blood sugar rise in rabbits.
Fig. 3. Blood sugar levels of baby rabbits housed at 32°C and exposed to high ambient temperature of 45°C for a period of 2½ hours with treatment by the ganglioplegic drug Anislysem, 0.4 mg./kg. body weight.
of exposure of baby rabbits controlled at 32°C to high ambient temperature of 45°C for 2½ hours on the blood sugar level in mg./100 ml. with treatment by the adrenergic blocking agent Ergotamine Tartrate, 50 µg/kg. body weight.
Khomrad and Loew (1951) further pointed out that these agents act by being adsorbed into liver cells and thus prevent epinephrine from stimulating glycogenolysis.

The pharmacological properties of pentolinium are similar to those of hexamethonium, i.e., its primary activity is ganglionic blockade. The ganglioplegic agent "Ansolyson" has been preferred to hexamethonium as it was reported by Roman and Wien (1955) that pentolinium tends to have an activity 6 times that of hexamethonium on sympathetic ganglia in the cat. From the results obtained with pentolinium tartrate, it is clear that liver glycogenolytic responses are a result of increased liver cell metabolism as a result of increased temperature. There is no apparent sympathetic or parasympathetic effect of these agents.

The thermoglycemic response of birds and mammals may be interpreted to be mediated by the adrenergic system.

Summary

Pigeons and baby rabbits show a significant thermoglycemic response to higher ambient temperature. An attempt has been made to study the role of the adrenergic system in the thermoglycemic response. The ganglioplegic drug "Ansolyson" and adrenergic blocking agent "Ergotamine Tartrate" have been found to abolish the thermoglycemic response.