An. Inst. Biol. Univ. Nal. Autón. México 41, Ser. Biol. Exp. (1): 55-88, 7 figs., 1 lám. (1970)

A MODEL OF THE FUEL-TENSION REGULATORY SYSTEM

Radu Racotta *
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ABSTRACT

The model is a sketch of a (theoretical) physical device containing electric components, and is chiefly focused on the maintainance of glycemic homeostasis. It is mainly composed of DC motor-generator groups, electric circuits and storage batteries. The model represents the actions and interactions which regulate releasing, blood concentration and tissue utilization of: a. The main energetic fuels (glucose and free fatty acids); b. Certain substances directly involved in the metabolism of the former (triglycerides, glycerol, lactate and amino acids); and c. Some hormones whose actions are related to these regulation (insulin, glucagon, epinephrine, glucocorticoids, growth hormone and its releasing factor and corticotropin and its releasing factor). Nervous action is also indicated.

Some clue intracellular transformations in liver, muscle and adipose tissue, together with synthesis and utilization of storage material (glycogen, storage protein and fat) are modeled.

In the endocrine organs (endrocrine pancreas, neuroendocrine hypothalamus, part of the adenohypophysis, adrenal cortex and adrenal medulla) hormonal secretion is modeled.

Nervous system is considered as a black box whose inputs and outputs participate in the control of the system.

The general input of the system is represented by the sporadic ingestion of glucose, triglycerides and amino acids. The general output is represented by glucose and free fatty acid expenditure in muscle, and by glucose expenditure in the nervous system.

The model could be a very good mnemotechnic device. Further, it might be physically reproduced or be set up in an analog computer, and used as a research devise to obtain the trend in any of the variables when others are changed.

The explanatory text, quoting an ample bibliography, is at the same time a synthesis of the modern data on the problem.

RESUMEN

El modelo representa el esbozo de un dispositivo físico (teórico) que contiene componentes eléctricos y que está enfocado sobre todo hacia la conservación de la homeostasis glucémica. Está compuesto principalmente por grupos de motores generadores de corriente continua, circuitos eléctricos y acumuladores.

En el modelo se representan las acciones y las interacciones que regulan la liberación, la concentración sanguínea y la utilización tisular de: a. Los principales combustibles energéticos (glucosa y ácidos grasos libres); b. Ciertas substancias directamente involucradas en el metabolismo de esos metabolitos (triglicéridos, glicerol, lactato y aminoácidos); y c. Algunas hormonas relacionadas con estas regulaciones (insulina, glucagón, adrenalina, glucocorticoides, hormona de crecimiento

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y su factor liberador y corticotrofina y su factor liberador). Está indicada también la acción nerviosa.
Se modelan algunas transformaciones intracelulares claves en el hígado, el músculo y el tejido adiposo, junto con la síntesis y la utilización del material de reserva (glucógeno, proteínas de reserva y grasas).
Se modela la secreción hormonal de algunos órganos endocrinos (páncreas endocrino, hipotálamo neuroendocrino, parte de la hipófisis, corteza y médula suprarrenal).
El sistema nervioso se considera como una caja negra, cuyas entradas y salidas participan en el control del sistema.
La entrada general del sistema consiste en la absorción esporádica de glucosa, triglicéridos y aminoácidos, y la salida general en el consumo de glucosa y de ácidos grasos libres por el músculo y de glucosa por el sistema nervioso.
El modelo puede ser un excelente dispositivo nemotécnico. Además, podría ser reproducido por un modelo físico o bien introducido en una computadora analógica y utilizado como dispositivo de investigación para reconocer la tendencia de las demás variables al cambiar el valor de cualquier otra.
El texto explicativo, que cita una bibliografía amplia representa, al mismo tiempo, una síntesis de los datos modernos acerca del problema.

INTRODUCTION

Glucose, among the metabolites, plays a very important parth both as raw material and as fuel. Homeothermic vertebrates have developed in the course of their evolution the capacity of maintaining a more or less constant level of glucose in their internal milieu. This level can be different according to the metabolic peculiarity of the species (Erlenbach, 1939; Nersesian-Vasiliu, 1968; Zelnícek, 1968).

The normal glycemic level most likely ensures good working conditions for the central nervous system, which can normally utilize only glucose as a fuel (Openshaw and Bortz, 1968; Unger, 1966). This normal glycemia is primarly assured by the existence of three possible glucose sources: ingested carbohydrates, gluconeogenesis and glycogen reserves.

Glycogen reserves are relatively scanty, and can theoretically last only a few hours as the unique energetic sources (Cahn, 1956). Gluconeogenetic productivity being rather small, the organism can utilize in certain conditions the lipid reserves, which are much more abundant. The circulating and readily utilizable form of neutral lipids are the free fatty acids (FFA). If mammals can not directly transform FFA into glucose, they can spare the latter utilizing the former to fulfill the metabolic needs of muscle, which is the greatest consumer (Ryan, 1966).

In a general way, the moment to moment regulation of fuel concentration necessary to the good working of the various consumers is achieved by: a. action of the main fuels, glucose and FFA, upon their own production and utilization and that of the other; b. action of a series of hormones, and; c. direct or indirect control of the nervous system.

To understand how the whole system works is not easy due to its complexity, but perhaps also to the countless unrelated experimental data. In the last ten years some interesting cybernetic (Goldman, 1960; Mc Lean, 1964), or mathematical (Ackerman *et al.*, 1965; Gatewood *et al.*, 1968) models of the glycemic regulation were published.

We tried to design a somewhat different model, which should fulfill some basic conditions:

1. The model should be a physical one, so that it could be, in principle, tested for its agreement with the original. In this way, its usefulness could be more than didactic. After several attempts to design a hydraulic, an electronic and a different kind of electric model, we came to the one we are presenting here.

2. An essential parameter around which all the system is whirling must be chosen, in order to circumscribe the model between acceptable limits. This parameter came out easily to be the normal blood concentration of glucose, and all the system should work in such a way to assure it.

3. We ought to represent the minimum indispensable phenomena necessary to the working of the system.

In the design of the model we needed to take into account the possible variations of the biological original, depending on the various conditions that are imposed to it. Many experimental data are obtained on animals (or humans) after a prolonged ingestion of deficient diets, after inanition, or during obesity, diabetes, the lack of one or more endocrine glands, etc. These data often reflect a particular aspect of a qualitative modification of the whole metabolic system, which is due to enzymatic restructurations that cope with the new general conditions (Birkenhager and Tjabbes, 1969; Braun *et al.*, 1967; Onicescu and Radu, 1969; Szepesi and Freedland, 1968). For instance, the different responses of perfused organs isolated from animals in normal or abnormal physiological conditions prove the existence of adaptative mechanisms at the cellular level. We think that such local changes are interdependent with the whole system modification. In order to keep our model as simple as possible, we did not try to account for all the known abnormal conditions, but only for the normal metabolic regulation.

THE CONTENT OF THE MODEL

The absolute need to simplify lead us to leave out organs and phenomena which do not seem to be quite esential to the working of the system. We present in brief what we are and what we are not modeling.

1. *Phenomena*

We model the actions and interactions which regulate releasing, blood concentration and tissue utilization of: a. The main energetic fuels (glucose and free fatty acids); b. Certain substances directly involved in the metabolism of the former (triglycerides, glycerol, lactate and aminoacids) and; c. Some hormones whose actions are related to this regulation (insulin, glucagon, epinephrine, glucocorticoids, growth hormone and its releasing factor, and corticotropin and its releasing factor). Nervous action is also represented.

We consider a living organism in normal physiological conditions, having intermitent periods of external energetic supply (food ingestion), and being in rest or in moderate muscular activity.

We model some intracellular conversions, but not enzymatic mechanisms in detail. Only storage material biosynthesis (glycogen, fat and storage protein), and only oxidation of glucose and fatty acids in muscle and of glucose in the nervous system are modeled. We did not include in the model the control of ingestion, the local aspects of intestinal absorption and correlated events.

2. *Organs and glands, and their function*

Liver. We model glycogen production from glucose or from non glucidic pre-

cursors as well as blood glucose production from glycogen and the same precursors; triglyceride production from glycerol and free fatty acids; the obligatory (portal) passing through the liver of ingested glucose and of the pancreatic hormones as well as the liver control upon the blood concentration of these hormones.

We do not model: liver fat and protein storage; biliary excretion of glucose excess; hepatic control upon the blood concentration of the other hormones; other hepatic functions.

Muscle. We model glucose storage as glycogen; blood lactate production; glucose and free fatty acids combustion with production of mechanical work; protein storage and liberation of amino acids.

We do not model specific muscular fat storage.

Adipose tissue. We model the storage of the triglycerides comming from the blood and of those locally synthetized; glycerol and free fatty acid production from triglyceride reserves; fatty acid re-esterification; glycogen storage.

Nervous system. We consider a black box in which three groups of activity are individualized: a. Secretion of corticotropin- and of growth hormone-releasing factors; b. Control of epinephrine production, and; c. General control of fuel metabolism. For simplicity sake, nervous action, in contrast with the rest of the model, has not an electric but a cybernetic representation.

We model the nervous utilization of glucose. All the other nervous actions are not represented.

Endocrine pancreas. We model insulin and glucagon production (not intestinal glucagon).

Hypophysis. We model only corticotropin and growth hormone production.

Adrenal cortex. We model only glucocorticoid production.

Adrenal medulla. We model only epinephrine production.

Generally speaking, hormone synthesis is not distinguished from secretion. As we did not model hormonal actions that do not seem to be directly correlated to the system, thyroid was not introduced in the model. We do not model renal excretion of glucose, as it does not occur in physiological conditions.

THE LOGIC OF THE MODEL

The model, through its logic, must ensure the following:

1. The representation by an adequate entity of the concentration of the following kinds of substances. *

–type A_1, $A_2 \ldots A_i$ –6 circulating metabolizable substances, i.e. glucose, free fatty acids, triglycerides, amino acids, lactate and glycerol.

–type B_1, $B_2 \ldots B_i$ –2 non circulating metabolizable substances, i.e. glycogen and protein.

* The following abbreviations will be used throughout the work: amino acids, *AA*; acetyl-CoA, *Ac*; corticotropin, *ACTH*; adenosine triphosphate, *ATP*; glucocorticoids, *Cs*; corticotropin-releasing factor, *CRF*; epinephrine, *E*; fatty acyl-CoA, *FA*; free fatty acids, *FFA*; glucose, G; glucagon, *Gg*; growth hormone, *GH*; glycogen, *Gln*; glycerol,*Gol*; glyceraldehyde phosphate, *G3P*; glucose 6-phosphate, *G6P*; glycero phosphate, *GoP*; growth hormone releasing factor, *GRF*; insulin, *Ins*; lactate, *L*; protein, *P*; pyruvic acid, *Py*; triglycerides, *Tg*.

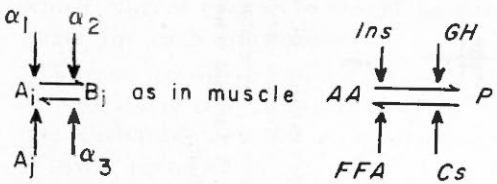
—type a_1, a_2 ... a_i —7 clue non circulating intermediary metabolites, i.e. glucose 6-phosphate, glyceraldehyde phosphate, pyruvic acid, glycero phosphate, acetyl-CoA, fatty acyl-CoA and adenosine triphosphate.

—type α_1, α_2 ... α_i —8 circulating non metabolizable substances (hormones), i.e. insulin, glucagon, epinephrine, glucocorticoids, corticotropin, growth hormone, corticotropin-releasing factor and growth hormone-releasing factor.

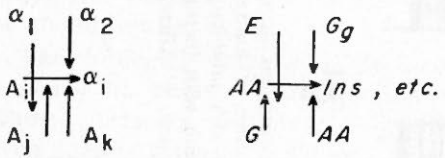
2. The reversible or non reversible conversion of one substance into another, either *directly*, following schemes of this kind:

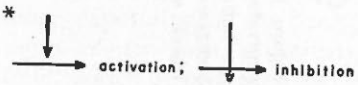
$A_i \rightarrow A_j$ as in liver: *FFA* → *Tg*
$a_i \rightarrow a_j$ as in muscle: *G6P* → *G3P*
$A_i \rightarrow a_i$ as in adipose tissue: *FFA* → FA, etc.

or under the influence of some activatory or inhibitory substances, following schemes of this kind: *

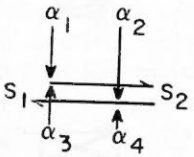


or as in pancreas





3. The independent structural maintainance of hormones so that, a conversion of the general type:



does not result in substances of the type:

$$T_i = \alpha_i + \alpha_j \quad \text{or} \quad T_j = S_i + \alpha_i$$

4. The storage of some metabolizable substances in specifical stores, whose charge and discharge must be possible even against a concentration gradient, under the influence of other substances.

These drastical conditions could be achieved by a quite unaccustomed type of electrical model formed of electrical DC machines, devices, storage batteries and circuits, which can make various systems whose functional logic is very closely connected with the functional logic of the original system.

In our model each substance of type A_i, B_i, a_i and α_i is represented by an electrical circuit, whose voltage represents the concentration of the respective substance. The enzymatic conversions are modeled by DC motor-generator groups (Fig. 1*a* and *b*). If the conversion is reversible (Fig. 1*b*), the rotors of both machines are rigidly coupled to one another. In this case, the character of motor or generator is not stable. Without changing the spin, each of the two machines can be motor or

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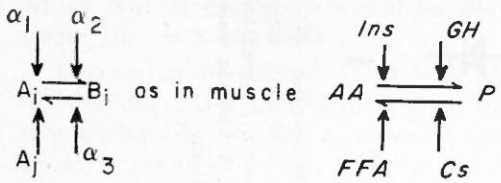

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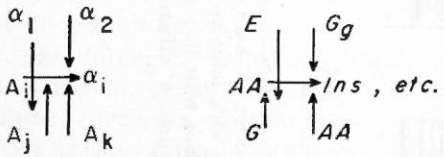

* activation; inhibition

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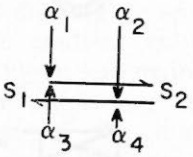

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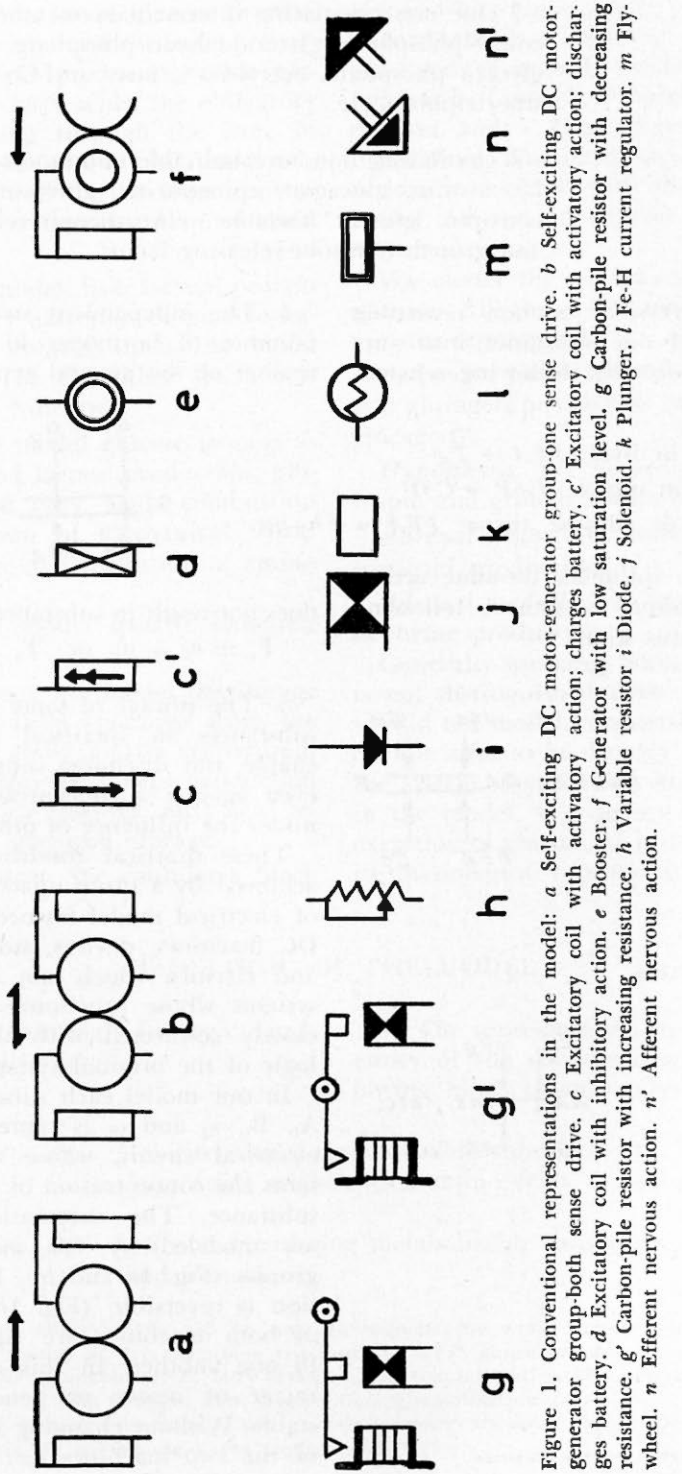


Figure 1. Conventional representations in the model: *a* Self-exciting DC motor-generator group-one sense drive. *b* Self-exciting DC motor-generator group-both sense drive. *c* Excitatory coil with activatory action; charges battery. *c'* Excitatory coil with activatory action; discharges battery. *d* Excitatory coil with inhibitory action. *e* Booster. *f* Generator with low saturation level. *g* Carbon-pile resistor with decreasing resistance. *g'* Carbon-pile resistor with increasing resistance. *h* Variable resistor *i* Diode. *j* Solenoid. *k* Plunger. *l* Fe-H current regulator. *m* Flywheel. *n* Efferent nervous action. *n'* Afferent nervous action.

generator according to the torque ratio between them. If the conversion has only one sense, the two rotors are coupled trough a free-wheeling roller clutch, and only one machine can drive the other. The energy supplied by the circuit of the motor to the circuit of the generator represents the conversion of one substance into another.

According to the manner in which the excitatory magnetic field is formed, there are many types of DC machines. To make the model easier to understand, and to achieve some advantages presented below, all electrical machines, in our model, have in series self-excitation; that means the whole current passing through the machine forms the self-excitatory magnetic field. However, a special study made *ad hoc* (but which exceeds the pure qualitative aspect of the presented model) can determine which type of excitation would be adequate for each conversion.

The action of substances of type A_i or α_i on these conversions is modeled by one excitatory coil for each substance at each point of action (Fig. 1*c* and *d*). According to the sense of the magnetic field produced (which can increase or decrease the main magnetic field produced by the series self-excitation coil), the substance has an activatory or an inhibitory action.

The biological substance stores are modeled by means of storage batteries whose charge or discharge is possible even against a tension gradient. This is achieved by small generators —*boosters*— (Fig. 1*e*) connected in series with the storage battery and its generator (which during discharge becomes motor), and rigidly coupled to the latter. The voltage of the booster, only a part of the total battery voltage, has a variable value and sense, depending on the strength and the sense of its own excitatory magnetic field, which is produced by various substances. By changing the sense of the magnetic field in the booster one changes the sense of its voltage, and implicitely the battery passes from charge to discharge or vice-versa. By increasing or decreasing the magnetic field, the strength of the charging or discharging current varies. In this manner, the action of *mediator* substances is modeled (Fig. 1*c* and *c'*), without their being mixed, each circuit maintaining its independence. In the absence of *mediators*, the booster voltage is zero, and the charging or discharging action is subject only to the gradient existing at each moment between the main supply (generator) and the storage battery.

The logic of the model adopted allowed us to realize some special cases as:

a. Groups of two cross-excited coupled motors and one generator (i.e. the main current of one motor passing through the main excitation coil of the other motor), representing *Tg* production from *FFA* and *Gol* in liver and adipose tissue. Since the excitation is crossed, *Tg* current is produced only if both constituents, *FFA* and *Gol*, are present, and only to the extent in which they are present in a determined ratio.

b. Groups of one motor and two coupled generators, representing *FFA* and *Gol* production from *Tg* in adipose tissue, and *Py* and *ATP* production from *G3P* in muscle. As in the former type, the two generators are cross-excited by the main excitation coil of the other circuit. In this manner, the production of *FFA* and *Gol*, and of *Py* and *ATP* respectively, is simultaneous and in a determined ratio.

c. Groups of two independent motors and one generator, representing *G3P* independent production from *L* or from *AA* in liver, and *ATP* independent production from *G3P* or from *Ac* in muscle. We encounter here the *differential*

gear effect, characteristic for two DC motors with series excitation, connected to one another also in series. Each motor increases its speed until it takes over its own part from the resistant torque. If the two rotors are rigidly coupled, and this is the case in our model, the speed is common and each motor takes over its part in the general *G3P* or *ATP* production, proportionally to the amount of *L* and *AA*, or *G3P* and *Ac* respectively, available in the system.

d. Generator with low saturation level (Fig. 1*f*), representing in adipose tissue the self-limited *FA* production.

Carbon-pile resistors (Fig. 1*g* and *g'*) model the variable facilitated passage of *G* across muscle, adipose and some nervous cell membranes. The sense of variation is represented by the sense in which the lever acts, the carbon-pile decreasing its resistance by compression.

Variable resistors (Fig. 1*h*) are located on the feed-back circuits which influence the production of pituitary hormone currents. A similar variable resistor models *G* expenditure in the nervous system.

Two diodes (Fig. 1*i*) are used in adipose tissue to direct the discharge of the *Tg* battery.

By solenoids it was modeled:

a. The action of *mediator* currents upon the levers of the carbon-pile resistors (Fig. 1*g* and *g'*).

b. The modification of the value of *G* excitatory current in pancreas. The *Cs* and *GH* solenoids can rotate the plane of the *G* coil in the *Ins* generator, varying thus the voltage produced by this generator, without changing the excitatory field of the *G* coil.

c. The current expenditure representing mechanical work by the plunger attracting solenoid in muscle (Fig. 1*j* and *k*).

Two Fe-H current regulators —*amperites*— (Fig. 1*l*) are in series on the *Ins* and *Gg* hepatic derivations. They *buffer* the changes in intensity of *Ins* and *Gg* currents that pass beyond the liver.

On some hormonal derivations there are series motor-generator groups, whose motor is coupled to a large fly-wheel (Fig. 1*m*). The generator can supply current only after a certain time, when the fly-wheel inertia has been overcome. This attempts to model the retarded hormonal effects that are achieved through induction or repression of enzyme synthesis.

Nervous action is simply represented by arrows (Fig. 1*n* and *n'*): centrifugal ones influencing the current "passage" across a motor-generator group or the resistance value in the variable resistors, and centripetal ones transmitting informations to the nervous system black box. This was done in order to avoid the extreme complication of the model that will result if different sensors (ammeters, strain gages, etc.) were introduced instead of the afferent arrows, and more effector coils instead of the efferent arrows.

ANALYSIS OF THE MODEL

A. *Fuel circulation*

Fig. 2 shows the modeled circulating substances (of type A_i and α_i), and the organs from which they are produced or on which they work. As it was already mentioned, three of the circuits —*G*, *Tg* and *AA*— are potentially connected to three virtual external generators. This represents the penetration of these metabolites in the internal milieu through intestinal absorption. In the interval of

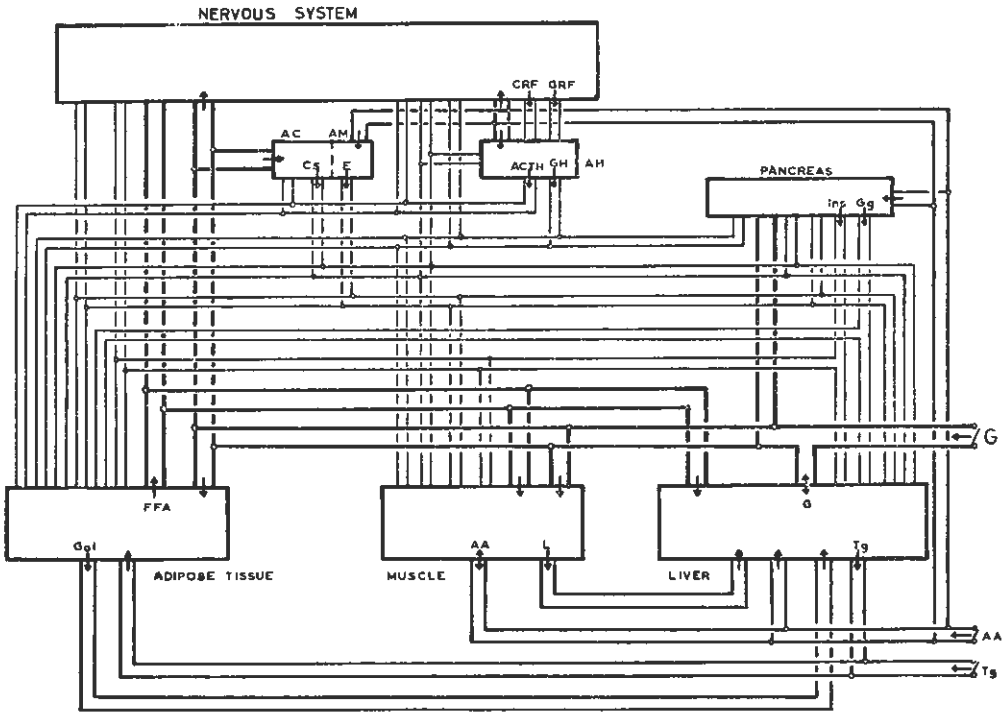


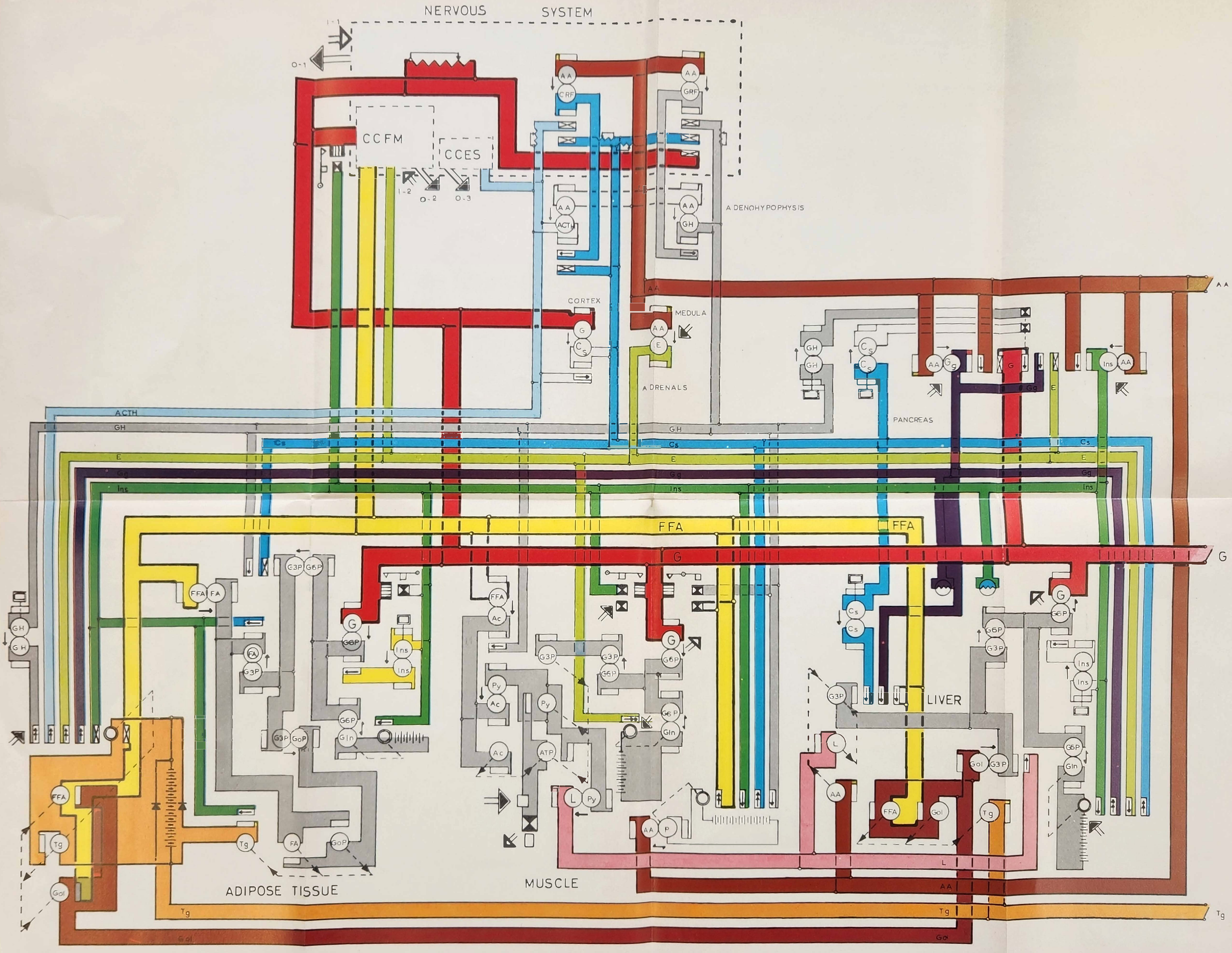
Figure 2. General representation of the model, showing the organs as black boxes (*AC*, adrenal cortex; *AM*, adrenal medulla; *AH*, adenohypophysis), and the following *general* circuits: *Fuels*: *G*, glucose; *FFA*, free fatty acids. *Metabolites*: *AA*, amino acids; *Tg*, triglicerides; *L*, lactate; *Gol*, glycerol. *Hormones*: *CRF*, corticotropin-releasing factor; *GRF*, growth hormone-releasing factor; *ACTH*, corticotropin; *GH*, growth hormone; *Cs*, glucocorticoids; *E*, epinephrine; *Gg*, glucagon; *Ins*, insulin. *G*,*AA* and *Tg* circuits can have an external origin too, eventually shorth-circuited. Arrow from a circuit to a black box shows that the substance is subjected to a conversion in this particular organ. Arrow from a black box to a circuit shows that the substance is produced in this particular organ. Circuit entries without arrows show that the substance has only activatory or inhibitory actions upon one or more conversions inside this particular organ.

no external current provision the three circuits are short-circuited at this level.

G passes necessarilly through the liver (in series), being afterwards distributed throughout the whole system (the subsequent derivation in parallel through the hepatic artery was not represented).

G tension represents the constancy parameter of the system. If and when external current production is large, this constancy is disturbed for a while, tension in *G* circuit increases uniformely throughout the system (Steele *et al.*, 1968) which results in the charge of *Gln* storage batteries in the liver, muscle and adipose tissue. As their capacity is limited (depending also on their charge at that moment), a simultaneous slower process of adipose *Tg* battery charge can occur. This battery can also be subsequently charged at the expense of the adipose *Gln* battery (Shapiro, 1965).

When *G* tension has returned to normal, its maintainance is achieved mainly by hepatic glycogenolysis and gluconeogenesis, that supply the *G* ex-



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DESIGNED: R RACOTTA & A. CIURES

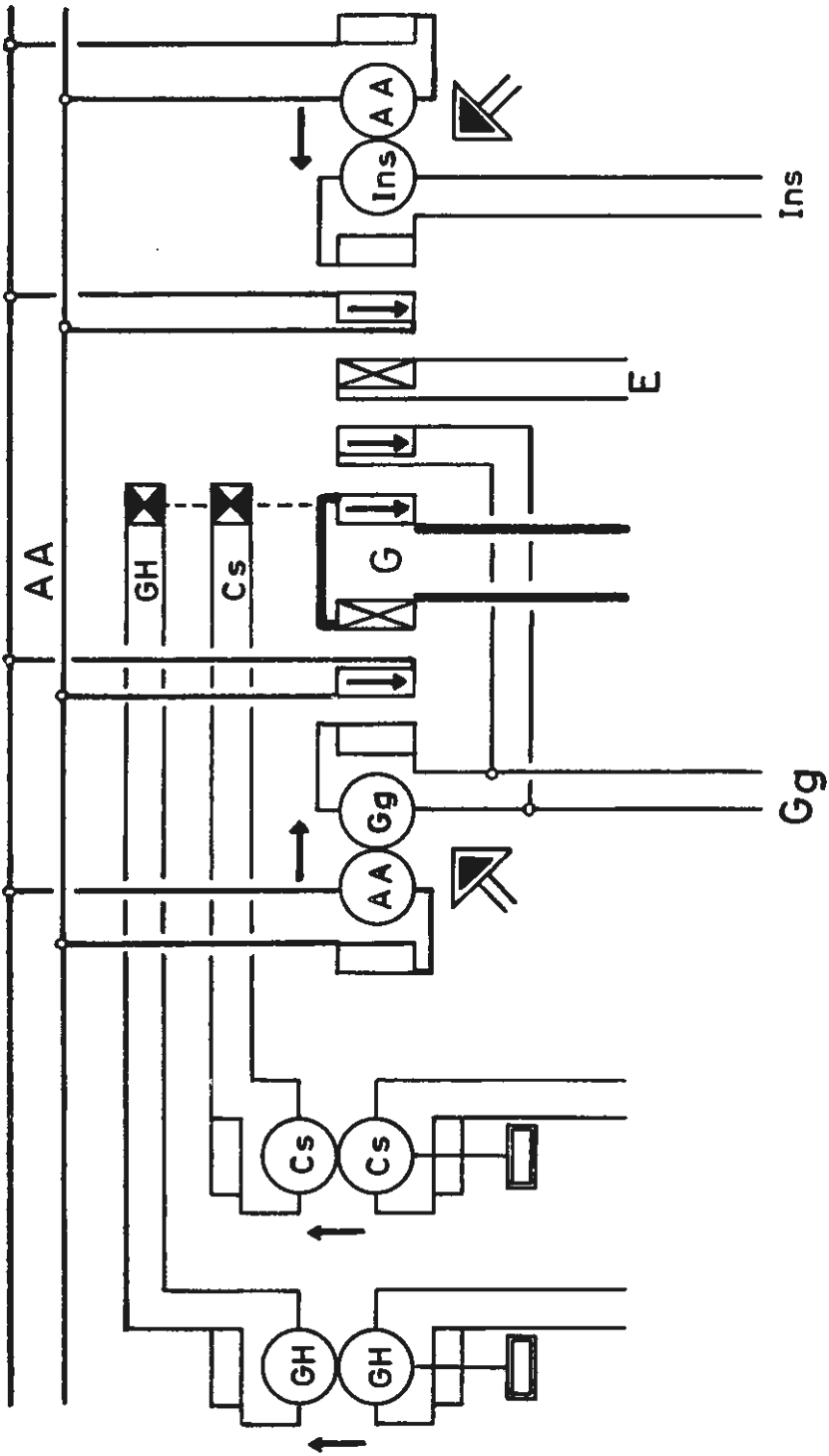


Figure 3. Model of the endocrine pancreas. General circuits as in Fig. 2.

penditure of muscle and nervous tissue. Muscular *G* consumption partly furnishes *L* current which is transformed again in *G* at the hepatic level. In that way, in the interprandial periods the unique *G* source is the liver.

Tg current charges directly the adipose *Tg* battery. When this discharges, it furnishes *FFA* and *Gol* currents in a constant proportion. *FFA* can either turn in the same tissue to recharge the battery, or pass into the *FFA* pool (circuit). The *FFA* circuit derivation going to muscle represents the main form of lipid utilization (Carlson, 1967; Ryan, 1966; Shapiro, 1965). Another *FFA* derivation goes to liver where it couples with the *Gol* current to restore the *Tg* current. The *FFA* tension is normally 50 times lower than the *G* tension, but it has a much wider range of variation (Paul *et al.*, 1966; Steffens, 1967).

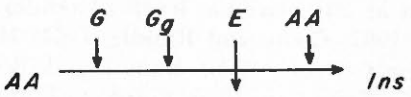
All the *Gol* current originating from adipose *Tg* battery discharge passes into the *Gol* circuit (Hagen and Hagen, 1964; Shapiro, 1965), and is utilized in the liver (Bergman, 1968; Hagen and Hagen, 1964) where it formes *G* (through intermediary circuits) or *Tg* (in conjunction with *FFA*). Hepatic formed *Tg* passes into the *Tg* circuit and charges the adipose *Tg* battery.

A small part of the *AA* current is derived to the glands where it produces hormonal currents, but most of it goes to muscle where it charges the *P* battery. In interprandial periods the *AA* necessity is covered by the discharge of this battery (*AA* production from other precursors was not modeled). The hepatic derivation of the *AA* circuit furnishes finally *G*.

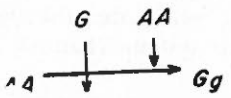
Other metabolic circuit entries in Fig. 2 represent regulatory derivations. The same figure shows hormonal circuits with their organ of origin and their regulatory derivations.

B. *Endocrine pancreas*

A schematic representation of the events in our model of the endocrine pancreas (Fig. 3) is:



and:



Islet cells normally secret *Ins* in direct proportion (Coore and Randle, 1964; Grodsky *et al.*, 1967; Kanazawa *et al.*, 1968; Randle and Ashcroft, 1969), and *Gg* in inverse proportion (Buchanan *et al.*, 1969; Lawrence, 1966; Ohneda *et al.*, 1969) to blood *G* concentration. At least as far as *Ins* is concerned, there is a basal secretion until a certain glycemia is reached (Lacy *et al.*, 1968; Vranic and Wrenshall, 1968). Variations of glycemia in one or the other sense would determine hypersecretion of one of the two hormones (Sokal, 1966*a*; Unger and Eisentrant, 1965; Vance *et al.*, 1968).

Pancreatic hormones do not seem to exert a negative feed-back upon their own secretion (Colwell and Colwell, 1966; Malaisse *et al.*, 1967*a*), though the opposite view is also sustained (Sodoyez *et al.*, 1969). There is but now duly proven in many species that *Gg* has an *Ins*-secretory action (Campbell and Rastogi, 1966*a*; Deckert, 1968; Devrim and Recant, 1966; Grodsky *et al.*, 1967; Samols *et al.*, 1966; Simpson *et al.*, 1966; Sussman and Vaughan, 1967; Turner and Mc Intyre, 1966). This action is likely immediate, as soon as *Gg* is secreted from the alpha cells, considering the nearness of the two type of cells.

AA, at least some of them, enhance *Ins* and *Gg* secretion (Floyd *et al.*, 1966; Ohneda *et al.*, 1968). That is modeled by the *AA* coils; the *AA* generators represent *Ins* and *Gg* synthesis.

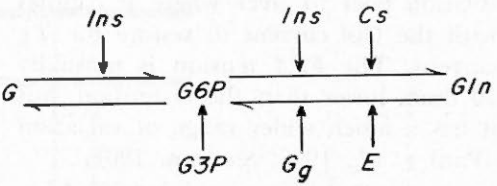
E stops in a persistent way *Ins* secretion at any glycemic level (Altszuler *et al.*, 1967; Coore and Randle, 1964; Hertelendy *et al.*, 1966; Kansal and Buse, 1967; Kris *et al.*, 1966; Porte *et al.*, 1966; Senft *et al.*, 1968; Wright and Malaisse, 1968). On the other hand, if *E* has any effect upon *Gg* secretion, this seems to be rather a reflex one, through the central nervous system (Ezdinli and Sokal, 1966).

GH (Bouman and Bosboom, 1965; Campbell and Rastogy, 1966*b*; Malaisse *et al.*, 1968; Martin and Gagliardino, 1967) as well as *Cs* (Campbell and Rastogi, 1968; Malaisse *et al.*, 1967*b*; Sutter and Mialhe, 1968) have a positive action upon *Ins* secretion, but in a peculiar way. They seem to sensitize beta cells to *G*, increasing thus *Ins* to *G* ratio. That is modeled by two electromagnets on these hormonal derivations, modifying the plane of the *G* coil at *Ins* generator. These effects being delayed, and persisting after hormonal returning to normal blood concentration levels, a flywheel motor-generator group is represented on the pancreatic derivation of each of the two hormones.

The part played by the nervous system in the control of pancreatic hormones secretion is less evident. The fact that a transplanted pancreas succeeds in maintaining normal blood *G* levels (De Jode and Howard, 1966; Huguet *et al.*, 1969) speaks in behalf of an independence of the gland. Nevertheless, the existence of neuro-insular complexes (Morgan and Lobl, 1968) as well as a series of physiological experiments are in favour of a nervous control upon *Ins* secretion (Daniel and Henderson, 1967; Drzhevetskaya, 1965; Kaneto *et al.*, 1967; Malaisse *et al.*, 1967*c*; Porte and Williams, 1966; Sergeyeva, 1940), and upon *Gg* secretion (Ezdinli and Sokal, 1966; Ezdinli *et al.*, 1968), though there are opposite results, too (Nelson *et al.*, 1967). We consider, in the model, that nervous system influences, at least in some instances, pancreatic hormone secretion through two centrifugal arrows acting upon the two generators.

C. *Liver*

A part of the transformations in our liver model (Fig. 4) are represented by the following scheme:



Concerning *G6P*, we did not take into account some recent works which question the necessity of passing through *G6P* for *Gln* synthesis (Antony *et al.*, 1969), or which suppose two or more cellular compartments for *G6P* (Threlfall and Heath, 1968; Zakim and Herman, 1967). These interpretations could nevertheless have a great importance in a more elaborate study of the hepatic glucoregulatory system.

Experiments on isolated perfused liver show that *G* penetration into the liver cell is enhanced by a high *G* concentration in the perfusate (Dorner *et al.*, 1968; Figueroa and Pfeifer, 1966). The permeability of the hepatocyte for *G* is very high (Park *et al.*, 1968), the sense of its transfer depending on its relative concentration on the two sides of the membrane, that is to say, on the relation between its phosphorylation and *G6P* hydrolysis (Randle, 1963). Nevertheless, some data show that *G* hepatic output is not influenced by a

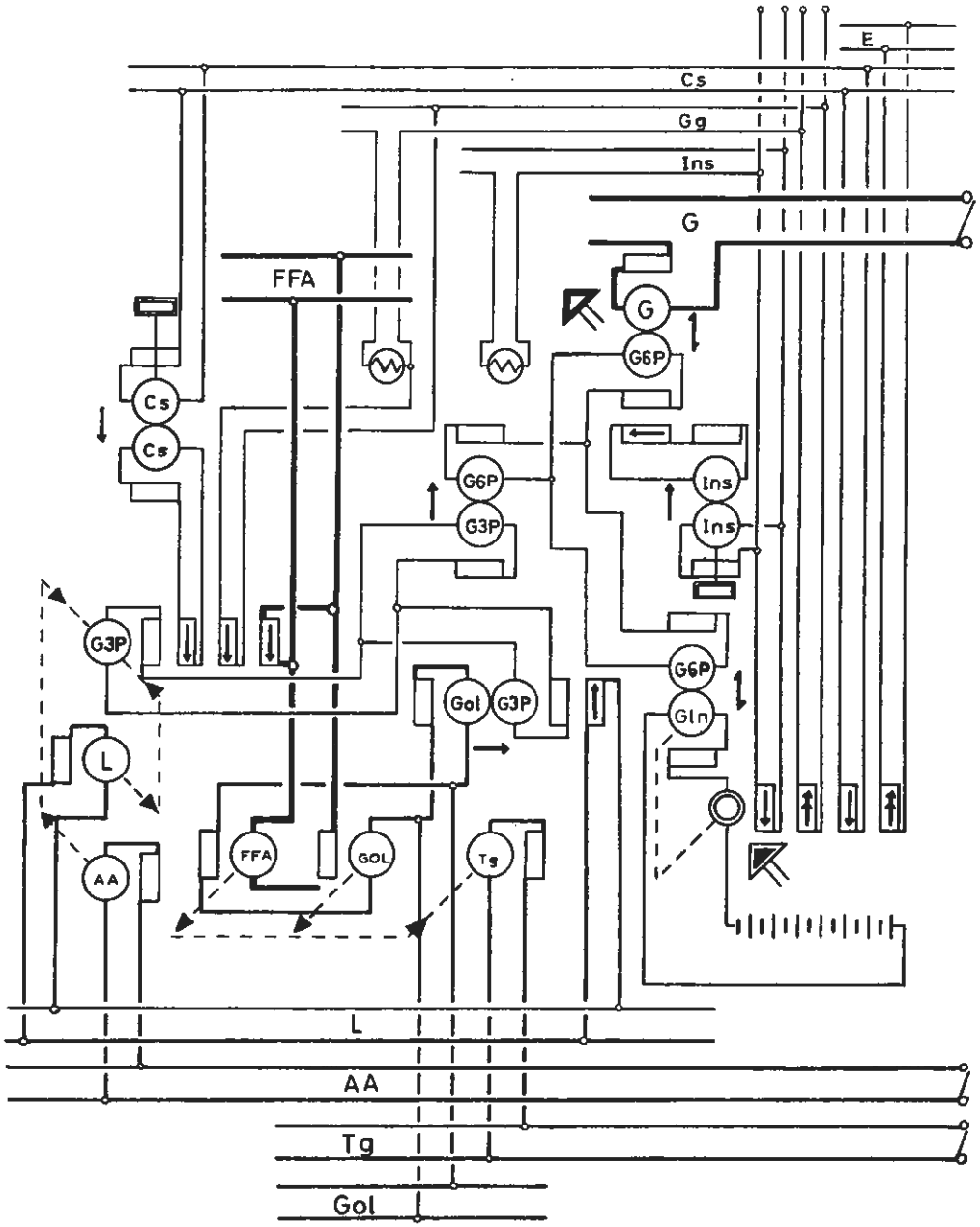


Figure 4. Model of the liver. General circuits as in Fig. 2. Local circuits: *Gln*, glycogen; *G3P*, glyceraldehyde phosphate; *G6P*, glucose 6-phosphate.

low concentration in the perfusate (Sokal and Weintraub, 1966), and thus the opinion of a direct regulation of *G* input and output by blood *G* concentration (Glinsman *et al.*, 1969) is not so obvious.

The factors that regulate glucose 6-phosphatase activity are not well known. Since the group *G6P-Gln* is under a strong hormonal control, it results from the model that the input, but specially the output of *G*, could in fact be regulated by *G6P* tension, itself dependent on the *Gln* battery tension and on the hormonal action upon it.

Concerning the hormonal action at the hepatic level, we have to mention first the necessary passage of the two pancreatic hormones through the liver, before going into the general circulation. Liver controls in a significant manner the suprahepatic level of these hormones (Mortimore *et al.*, 1959; Sokal, 1966*a*; Waddell and Sussman, 1967), partly by biliary removal (Daniel and Henderson, 1968; López-Quijada and Goni, 1967). This fact could play a very important part in the general balance of the whole regulatory system, namely by an increase at some moments of the hepatic action of *Ins* and *Gg* in detriment of their extrahepatic ones. Some data support this point of view (Steele *et al.*, 1968; Voyles *et al.*, 1969). A similar phenomenon occurs experimentally when *E* is injected into the portal vein (Rodríguez-Zendejas *et al.*, 1968). We tried to model this liver action on *Ins* and *Gg* by passing each of the hepatic circuits of these hormones through a Fe-H current regulator (*amperite*) in series.

Ins does not seem to control *G* passing across the hepatic cell membrane (Williams *et al.*, 1968*b*), but rather to be indispensable for the induction (flywheel motor in the model) of this enzyme (Niemeyer *et al.*, 1967). *Ins* coil at this level could not be very strong since other works show that *G→G6P* reaction can take place in the absence of *Ins*, perhaps by an inversion of the glucose 6-phosphatase reaction under blood *G* tension influence (Friedmann *et al.*, 1967*a*; Nordlie *et al.*, 1968).

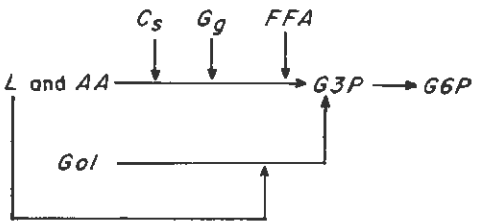
The booster of the *Gln* battery is controled by four coils. *Ins* and *Cs* enhance *Gln* synthesis (Weber *et al.*, 1965). Concerning *Cs*, some authors think that this is their primary and specific hepatic effect (Oji and Shreeve, 1966). On the other hand, there are claims that the effect could not be a direct one since it does not occur in *in vitro* preparations (Meiers *et al.*, 1967; Staib *et al.*, 1967). An explanation of this contradictory results could consist in a reciprocal potentiatory action of the two hormones at this level (Friedmann *et al.*, 1965; Kreutner and Goldberg, 1967), which was not represented in the model.

The powerful and fast glycogenolytic action of *Gg* is well established (Ezdinli and Sokal, 1966; Lefebvre, 1968; Shoemaker *et al.*, 1959; Weintraub *et al.*, 1969). *Gg* appears to be indispensable for *G* production from hepatic *Gln* (Sokal and Weintraub, 1966).

E glycogenolytic effect (Craig and Honig, 1963; Northroi, 1968) could be obtained, according to some data, only by administrating unphysiological hormonal doses (Ezdinli and Sokal, 1966; Sokal *et al.*, 1964). Though both *Gg* and *E* glycogenolytic effects are mediated through cyclic adenosine monophosphate, they seem to be independent (Sanbar, 1968), and to act through somewhat different ways (Bitensky *et al.*, 1968).

Mammals synthetize *G* from many precursors: other glucides, intermediary glycolytic metabolites, amino acids, glycerol (Krebs *et al.*, 1969; Ross *et al.*, 1967 *b*; Weidemann and Krebs, 1969).

In the model, all sugars were included in the G current. Pyruvic acid is easily convertible into lactic acid, which circulates as *L*. Thus, we only represent *L*, *AA* and *Gol* as precursors of G, the three producing *G3P* as a common intermediary metabolite. The scheme of this process, as represented in our model, is:



L→*G3P* and *AA*→*G3P* conversions are represented by a special group containing two independent motors and one generator. Gluconeogenesis rate from *AA* is directly dependent on the *AA*-and inversely dependent on the *G-blood* concentration (Herrera *et al.*, 1966; Ruderman and Herrera, 1968). In the model, indeed, *AA*→*G3P* as well as *L*→*G3P* conversion will primarly depend on the *AA*/*G6P* and *L*/*G6P* respective tension relationships.

FFA enhance gluconeogenesis at the pyruvic acid level (Ashmore and Weber, 1968; Friedmann *et al.*, 1967*b*; Jagow *et al.*, 1968; Ross *et al.*, 1967 *b*; Teufel *et al.*, 1967).

Ins inhibits gluconeogenesis (Shrago *et al.*, 1967; Weber *et al.*, 1965), but it seems to be rather an indirect effect through a fall of *FFA*- and/or of *AA*-tension (Snipes, 1968).

Gg seems to be the most potent gluconeogenetic agent at the pyruvic level, too (Ashmore and Weber, 1968; Exton and Park, 1966; Ezdinli and Sokal, 1966; Sokal, 1966*b*; Teufel *et al.*, 1967). Since its action at this level appears only after *Gln* depletion (Ross *et al.*, 1967*a*), its *Gln*-acting coil could be much stronger than the G3P-acting one.

The mechanism of the *Cs* gluconeogenetic effect is a controversial issue, mainly because it does not occur in a perfused liver which does not proceed from an animal previously treated with these hormones (Staib *et al.*, 1967). This suggests that the main effect is due to enzymatic induction (Betheil *et al.*, 1965; Ewald *et al.*, 1963; Greengard *et al.*, 1963; Henning *et al.*, 1964). As this action is delayed, we modeled it through a fly-wheel motor. On the other hand, *Cs* have a hepatic and muscular proteolytic action (Bellamy, 1967; Bellamy *et al.*, 1968) which is represented in the muscle model.

Gol tension is generally proportional to adipose lipolysis, and this substance is integrally utilized in the liver (Bergman, 1968). *L* enhances *Gol*→*G3P* conversion (Ashmore and Weber, 1968; Ross *et al.*, 1967 *b*) *Gol* can produce mainly *G6P* (through *G3P*) and *Tg*. The sense *Gol* takes could depend in some measure on the *G* tension itself. At a low *G* and *Ins* (and hence *G6P*) tensions, the gluconeogenetic sense could prevail (Bergman *et al.*, 1968), while in hyperglycemic conditions the blockade of gluconeogenesis would orient *Gol* towards hepatic *Tg* production (Mackenzie *et al.*, 1968). It seems that high *Gol* and *FFA* tensions results always in producing hepatic *Tg*. In diabetes, increased *G* tension is accompanied by high *Gol* and *FFA* tensions, due to lack of available *Ins*. This brings about an excessive hepatic *Tg* production. An experimentally induced lipolysis has the same effect (Bizzi and Garattini, 1967; Bost *et al.*, 1967). Even in fasting, when there are favorable gluconeogenetic conditions, the high *Gol*- and *FFA*-tensions can simultaneously produce an increased hepatic fat concentration (Kenmoku and Iwao, 1966; Trotter, 1967).

We have already specified that hepatic fat storage and turnover, as well as

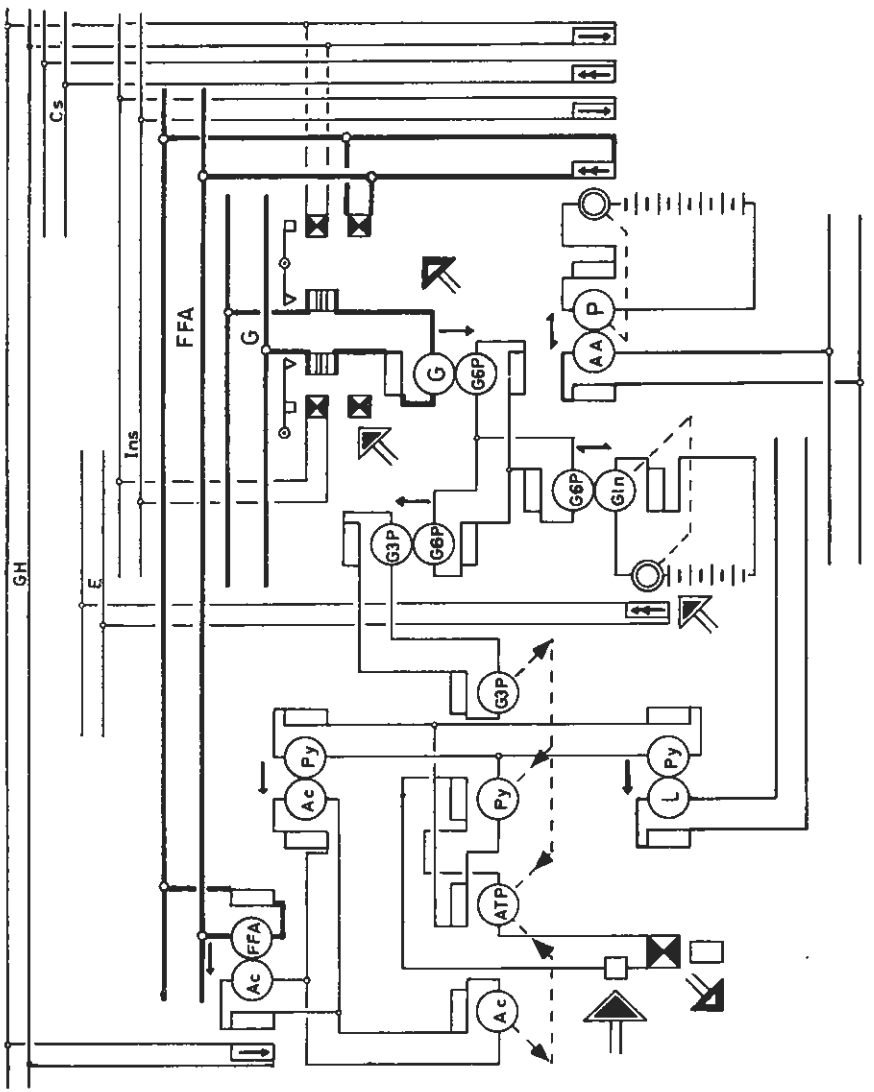


Figure 3. Model of the muscle. General circuits as in Fig. 2. Local circuits: *Ac*, acetyl-CoA; *ATP*, adenosine triphosphate; *Gln*, glycogen; *G3P*, glyceraldehyde phosphate; *G6P*, glucose 6-phosphate; *P*, protein; Py, pyruvic acid.

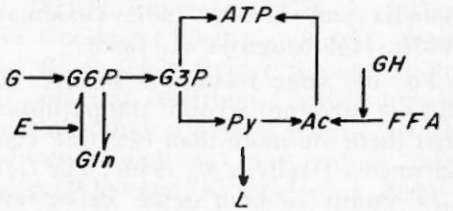
FFA and *Gol* synthesis from *G* will not be represented in the model. As a matter of fact, hepatic *FFA* synthesis seems to be small in comparison with that of adipose tissue (Leveille *et al.*, 1968), and hepatic *Gol* synthesis depends on gluconeogenetic requests (Frank *et al.*, 1968; Gericke *et al.*, 1968). In normal conditions, as represented in the model, the liver synthetizes *Tg* (from circulating *FFA* and *Gol*), most of which passes to the blood (Baker *et al.*, 1968; Shapiro. 1967). *Tg* synthesis is modeled by a group formed of two coupled motors and one generator, whose characteristics were already described.

The studies concerning nervous action upon the mentioned hepatic processes have a long history which begins with Claude Bernard. It seems to be proven that hepatic parenchymatous cells are innervated (Alvarez-Fuertes *et al.*, 1971; Nicolescu, 1958; Riegele, 1928; Tanikawa, 1968). Nervous efferents are acting upon *Gln* synthesis (Shimazu, 1967) and lysis (Ban, 1965; Il'in and Soliternova, 1968; Shimazu and Fukuda, 1965; Shimazu *et al.*, 1966). At the same time, the existance of hepatic receptors seems now to be indirectly (Ketterer *et al.*, 1967; Russek, 1967; Russek *et al.*, 1968) as well as directly (Niijima, 1969) proven.

We represented thus an effector nervous arrow acting upon the *Gln* booster, and an afferent nervous arrow, somehow imprecisely located, at the level of the *G-G6P* conversion. If it will be proven that the liver receptors sense *G* passage through hepatic cell membrane (Russek, 1971), it would be necessary to add a resistance on the *G* hepatic derivation, from which the centripetal nervous arrow should start.

D. *Muscle*

The general scheme describing *G* transformations in our muscle model (Fig. 5) is:



$G \rightarrow G6P$ is a one sense drive group due to glucose 6-phosphatase lack (Randle, 1963). Muscle hexokinase is very active, and the limiting factor for *G* incorporation is membrane permeability (Malaisse and Franckson, 1965; Park *et al.*, 1968). The facilitated transport of *G* depends on the facilitatory or inhibitory actions of other substances. This is represented in the model by two carbon-pile resistors in series on *G* muscular derivation: one can be acted on to diminish, the other to increase its resistance.

Ins intensifies *G* transfer through the resting muscle cell membrane (Christensen and Orskov, 1968; Park *et al.*, 1968; Pastan *et al.*, 1966), being the sole hormone which increases muscular *Gln* concentration in physiological doses (Davidson and Haist, 1968). The depancreatized animal oxidises less *G* (Issekutz *et al.*, 1967). The increase of *G* incorporation rate during exercise is not accompanied, however, by a significant *Ins* hypersecretion (Cochran *et al.*, 1966; Nikkila *et al.*, 1968; Rasio *et al.*, 1966). This could be, at least partially, explained by a stimulative effect of nervous action on *G* transfer (Heinz, 1967; Narahara and Cori, 1968). We represented an effector nervous arrow acting upon the same variable resistance as *Ins* does.

An inhibitory action of *FFA* on *G* transfer was modeled (Park *et al.*, 1968; Randle *et al.*, 1964), although there are contrary opinions, too (Gjedde, 1968; Schonfeld and Kipnis, 1968). On the same inhibitory resistance a *GH* effect was represented (Altszuler *et al.*, 1968;

Bolodia and Young, 1967; Goodman, 1967*b*; Holobaugh *et al.*, 1968).

For the same reasons as in liver we did not take into account the possibility that there are more than one *G6P* compartments (Dully *et al.*, 1969). The *G6P-Gln* group is both sense drive, and *G6P* tension seems to control the sense of the current flow (Holmes and Mansour, 1968).

As muscle does not furnish *G* circulating current, muscle *Gln* is relatively little diminished even in case of general *G* necessity, such as in prolonged starvation (Depocas, 1962). *Gln* battery discharge depends on the energy expenditure of muscle contraction: the *ATP* electromagnet switched-on by a special (motor) nervous action. The work performed by this electromagnet, which represents in fact all the contraction system, induces a tension fall in the *ATP* circuit which *sucks up G6P* current through the *G3P* or the *Ac* generator. This entails an increased blood *G* expenditure (Cochran *et al.*, 1966; Keul *et al.*, 1968; Rasio *et al.*, 1966). This expenditure is partially compensated by liver output (Issekutz *et al.*, 1967), but additional currents are provided by muscle *Gln* battery and by *FFA* circulating current.

The prolonged capacity of work of muscle seems to be entirely dependent on its *Gln* battery tension (Bengt and Hermansen, 1967; Bergstrom *et al.*, 1967). Once the battery is discharged, the *ATP* electromagnet could not function normally any more. This discharge, obviously dependent on the tension fall produced in the *ATP* circuit, is enhanced by *E* (Sokal and Sarcione, 1959; Svedmyr, 1965). *E* coil acts only at the *Gln* booster level, increasing *G6P* tension (Saha *et al.*, 1968), and not upon any of the intermediary glycolytic conversions (Karpatkin *et al.*, 1964; Wilkie, 1966). At the same time, nervous action itself promotes *Gln* battery discharge (Danforth and Helmreich, 1964; Posner *et al.*, 1965).

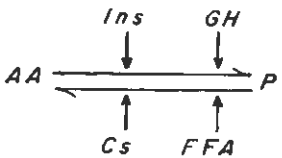
G3P produces in constant proportion, through a special group of one motor and two coupled generators, *Py* and *ATP*. Energy expenditure through the *G3P-ATP* group models anaerobic contraction. *L* is produced from *Py* in the resting as well as in the working muscle (Chapler and Stainsby, 1968).

Muscle can consume *FFA;* myocardial muscle utilizes them even preferably (Olson, 1967; Shipp *et al.*, 1961). It is not clear if muscular fat could be utilized as such (Carlson, 1967; Hagenfeldt and Wahren, 1968; Issekutz and Paul, 1968; Olson, 1967). *FFA* muscle utilization rate is normally in direct relation to their blood concentration (Armstrong *et al.*, 1961*a*; Hagenfeldt and Wahren, 1968; Steinberg, 1966), and in inverse relation to G concentration (Issekutz *et al.*, 1967). Muscular work is accompanied by an increased lipolysis which throws relatively important *FFA* amounts into the ciculation (Gollnick, 1967; Konttinen and Nikkila, 1964; Reinheimer *et al.*, 1968). Thus, the contribution of this fuel to muscle energy expenditure is considerably increased (Keul *et al.*, 1968; Paul and Issekutz, 1967). In the model, the muscle derivations of *FFA* circuit inhibit *G* transport across the membrane, on the one hand and, on the other, they transfer current through *FFA*→*Ac* motor-generator group, in direct proportion to the tension fall in *Ac* circuit and to the increasing tension in *FFA* circuit. The only favoring factor at the *FFA*→*Ac* level seems to be *GH* (Knobil and Hotchkiss, 1964).

The big efferent arrow that acts on *ATP* circuit represents motor nervous action that induces muscle contraction. *ATP* generator is coupled to two independent motors: *Ac* and *G3P*. An affe-

rent nervous arrow at the *ATP* electromagnet level represents the presence of mecano- and perhaps also chemoreceptors (Coote *et al.*, 1969). Another afferent nervous arrow, at the presumed level of *G-G6P* group, represents muscle glucoreceptors (Ivanov *et al.*, 1966; Krulich, 1957).

Reserve proteins (*P*) are modeled by a storage battery. The scheme of the conversions we model is:

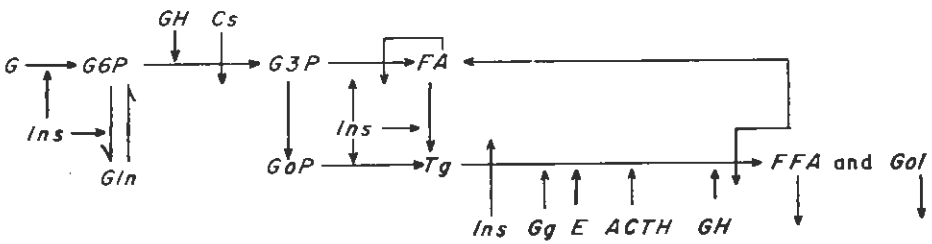


Ins and *GH* induce *P* synthesis (Narahara and Cori, 1968; Snipes, 1968); *Cs* (Friedmann *et al.*, 1965; Goldberg and Goodman, 1969), and *FFA* (Buse and Buse, 1967) induce proteolysis. In physiological conditions, during intestinal absorption, a high *G* tension, which induces a high *Ins* one, would thus charge *P* battery (Knippel *et al.*, 1969).

E. *Adipose tissue*

Adipose tissue represents a functional ensemble under neuro-endocrine control which acts, in turn, by its metabolites upon other tissues as well as upon the neuro-endocrine system itself (Liebelt *et al.*, 1965).

The transformations that are modeled (Fig. 6) could be represented by the following scheme:



So, *G* is finally transformed in *FA* and *GoP* (Foster and Katz, 1966; Katz and Rognstad, 1969), which combine in constant proportion to form *Tg*. An increased *FA* tension would have an inhibitory effect upon its own production (Bortz and Lynen, 1963). There are claims that this inhibition is exerced by *FFA* and not by *FA*, but in the doubt, and in order to simplify the model, we represented it by a *FA* generator with low saturation level in the *G3P-FA* group.

G transport across adipose cell membrane is facilitated by *Ins* (Crofford and Renold, 1965; Renold *et al.*, 1966; Rodbell, 1967), though the degree of this facilitation varies with the species (Bartos and Skarda, 1968; Mosinger and Kujalová, 1967). The same hormone seems to have a delayed (fly-wheel motor-generator group) inductive effect on hexokinase synthesis (Hansen *et al.*, 1967), and a promoting effect on *Gln* synthesis (Goodman, 1967*a*).

Adipose *Gln* battery is not of great capacity, and is charged to its full only in the case of a high general *G* tension (Goodman, 1967*a*). *G6P* current is strongly *sucked up* by the big *Tg* battery. *Ins* intervenes in this pathway, too (Armstrong *et al.*, 1961*b*; Takano *et al.*, 1967; Vrba, 1964, 1966). In this way, *Ins* actually facilitates all the ways of *G* utilization that lead to *FA* and *Tg* synthesis (Ball, 1965; Gliemann, 1968).

The big *Tg* battery can be charged either directly from the *Tg* circulating

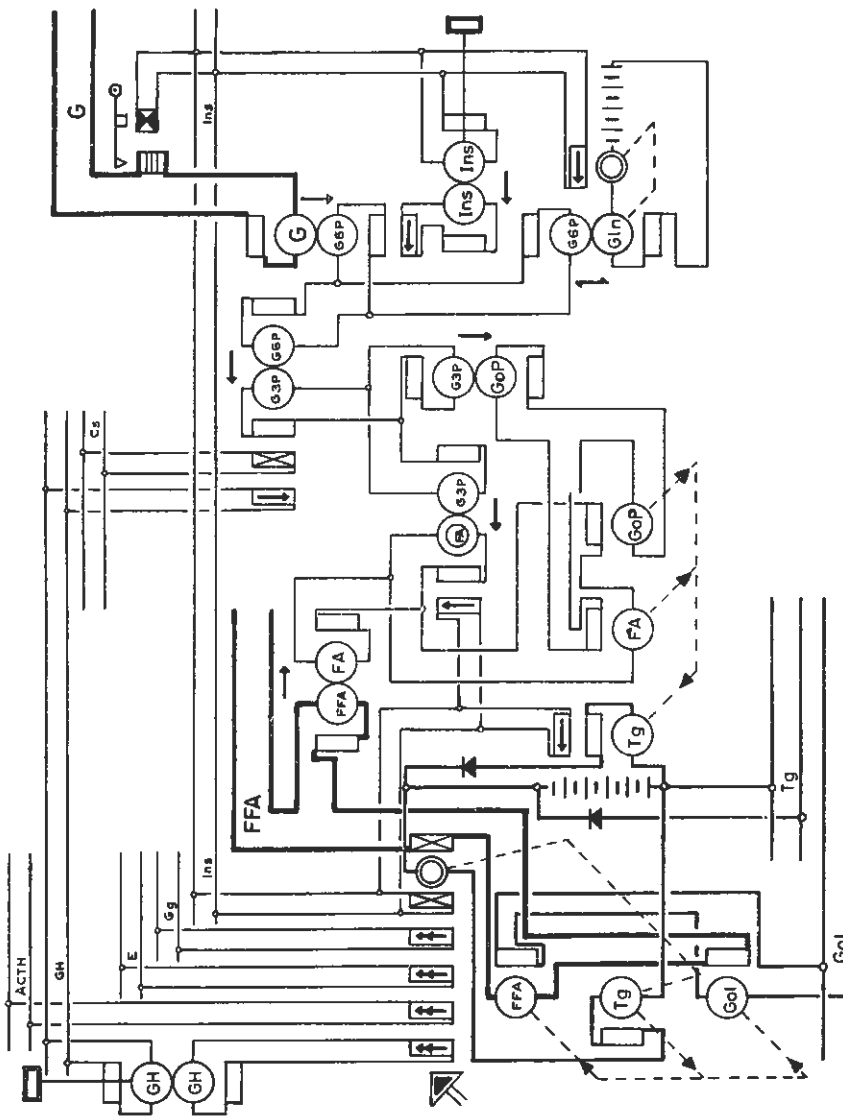


Figure 6. Model of the adipose tissue. General circuits as in Fig. 2. Local circuits: *FA*, fatty acyl-CoA: *Gln*, glycogen: *G3P*, glyceraldehyde phosphate: *G6P*, glucose 6-phosphate: *GoP*, glycerophosphate.

current, or through the two motors—(*FA* and *GoP*) one generator (*Tg*) group. At its turn, *FA* current could originate either from the *G3P* current, as we already saw, or from the *FFA* one. *Gol* current can not be employed to produce adipose *GoP* for lack of glycerol kinase (Shapiro, 1965).

Tg battery is discharged through an one motor-two generators group, usually furnishing in constant proportion *Gol* an *FFA* (lipolysis). Sometimes this proportion changes in favour of *FFA*, due to an incomplete hydrolysis of *Tg* to di— and monoglycerides (Havel, 1965; Scow *et al.*, 1965), but we did not consider this possibility in the model. Intracellular *FFA* seem to inhibit their own production from *Tg* (Bally *et al.*, 1965; Rodbell, 1965).

Lipolysis undergoes a strong hormonal influence (Lewis and Matthews, 1968) which is not understood in all its details. On this influence depends the intensity of *Tg* turnover.

Ins seems to have a direct inhibitory action on fat mobilization (Bally *et al.*, 1965; Blecher *et al.*, 1968; Havel, 1965; Jungas and Ball, 1963). *Gg* effect does not appear always clear *in vivo*, due to its hyperglycemic and hyperinsulinemic action, which promotes lipogenesis. Even *in vitro* the experimental results differ according to dose and species. Nevertheless, *Gg* seems to be, after all, a strong lipolytic agent in physiological doses (Bally, 1968; Lefebvre, 1968; Whitty *et al.*, 1969).

ACTH has a lipolytic action which is independent of its adrenocortical one (Akgun and Rudman, 1969; Benuzzi-Badoni *et al.*, 1968; Hynie *et al.*, 1968; Lebovitz *et al.*, 1965; Scow *et al.*, 1965).

As the action of *E* on *G* incorporation to adipose tissue is a subject of much debate (it has been considered activatory: Hagen and Hagen, 1964; Park *et al.*, 1968; inhibitory: Il'in and Soliternova, 1968; or nill: Rodbell, 1967) we did not model it. On the other hand, *E* is an efficient lipolytic agent (Bost *et al.*, 1968; Fain, 1967; Friedmann *et al.*, 1965; Svedmyr, 1967).

GH is generally considered as an important lipolytic factor *in vivo* (Luft and Cerasi, 1967; Mc Kee and Russell, 1968; Raben and Hollenberg, 1959; Skarda *et al.*, 1968). Some experimental data are however difficult to interpret: a. *GH* increases in a notable way, *in vitro*, *FA* synthesis (Goodman, 1967*a*); b. It lowers *in vivo* blood *FFA* concentration during the first 30 minutes that follow its administration (Sirek *et al.*, 1967, and; c. Its lipolytic effect comes late (Fain, 1967; Goodman, 1968*a*; Zahnd *et al.*, 1960). It is probable that *GH* acts upon more than one point and in different ways (rapid or delayed effects), and that, *in vivo*, its direct effects could be counteracted by the hyperinsulinemia it produces (Altszuler *et al.*, 1968). We modeled only a delayed effect on lipolysis, and an excitatory action on *G6P* utilization.

Besides the hormonal one, a nervous lipolytic action appears evident. Nervous terminations belonging to an intrinsec system surround the parenchymatous cells; this system looks anatomically independent to the orthosympathetic innervation, which is mainly vascular (Derry *et al.*, 1969). Norepinephrine is present in adipose tissue nerve terminations (Westerman and Stock, 1963); its concentration decreases by denervation (Sidman *et al.*, 1962), and increases during starvation (Sdrobici *et al.*, 1967). On the other hand, injected norepinephrine has a similar lipolytic effect as *E* (Hagen and Hagen, 1964). Stimulation of adipose sympathetic nerves *in vitro* brings about the appearing of *FFA* and *Gol* in the perfusion fluid (Fredholm and Rosell, 1968). *In vivo*, sympathetic activity increases blood *FFA*

concentration, even in adrenalectomized animals (Goldfien, 1966; Goldfien *et al.*, 1966). It seems that the sympathetic tonus in the adipose tissue controls the intensity of lipolysis (Goodner *et al.*, 1967).

All the mentioned effets upon lipolysis seem to be brought about through cyclic adenosine monophosphate (Butcher *et al.*, 1968; Meng and Ho, 1967; Turtle and Kipnis, 1967), but their detailed mechanisms might be different (Williams *et al.*, 1968*a*), and the various effects are species-dependent (Benuzzi-Badoni *et al.*, 1968; Burns and Langley, 1968; Langslow and Hales, 1969).

The level of blood *FFA* concentration can depend on their re-esterification rate, which depends on *G* and *Ins* blood concentration (Angel, 1969; Lewis and Matthews, 1968). When *G* supply is sufficient, *Tg* turnover is intensified at the expense of *G* which is consumed and of *Gol* which is liberated. We did not model a possible direct excitatory effect of *G* upon *FFA* re-esterification (Carlson, 1965). The energetic result of *FFA* re-esterification is a thermogenesis (Ball, 1965; Hagen and Hagen, 1964), modeled by an excessive functioning of the motor-generator groups that are involved in these conversions. On the other hand, *Gol* and excess *FFA* produce at the hepatic level *G* and *Tg*, intensifying in this way liver metabolism and *Tg* circulation (Steinberg, 1966).

We left the effect of *Cs* upon adipose tissue till the end, because of the difficulty to interpret it. Among the various hypothesis, we adopted the one which considers that *Cs* decrease *FFA* re-esterification rate (Jeanrenaud, 1967), perhaps by diminishing *G* utilization rate (Landau, 1965; Soliternova, 1968). The consequence of this would be an increase in blood *FFA* tension. We put a coil with inhibitory action on the way of *G* utilization at a very uncertain place (*G6P - G3P* group). Anyhow, if this interpretation is correct, for an efficient inhibition of *Tg* synthesis the blocking point will likelly be before the bifurcation point of *G3P* towards *FA* and *GoP*, as this latter substance appears to be the limiting factor of re-esterification (Mc Lean *et al.*, 1968).

F. *Nervous system*

Inside the *big black box* which represents nervous system in our model (Fig. 7), we individualized two *small black boxes*: one representing a *Center of control of fuel metabolism* (CCFM) and the other a *Center of control of epinephrine secretion* (CCES). Inside the black boxes one can imagine a net of circuits which integrate the received informations and command the efferent nervous actions. We also included into the nervous system the models of the secretory systems of two hypothalamic releasing factors, the ones for *GH* and *ACTH*.

We consider the following general inputs:

I-1. Unspecific afferentations. These represent all the sensory and propioceptive nervous inputs as well as hormonal and humoral actions which can influence in a reflex way the metabolic system that is modeled. They enter directly to the big black box.

I-2. Specific interoceptive afferentation. From hepatic and muscular glucoreceptors and from muscular chemoreceptors (centripetal arrows in Figs. 4 and 5) entering CCFM.

I-3. Circulating substances.

G is practically the only fuel which nervous system can utilize (Openshaw and Bortz, 1968), and it also plays an important rôle in the metabolism of the nitrogenated substances (Otsuki *et al.*, 1968). As a result, two thirds of the basal

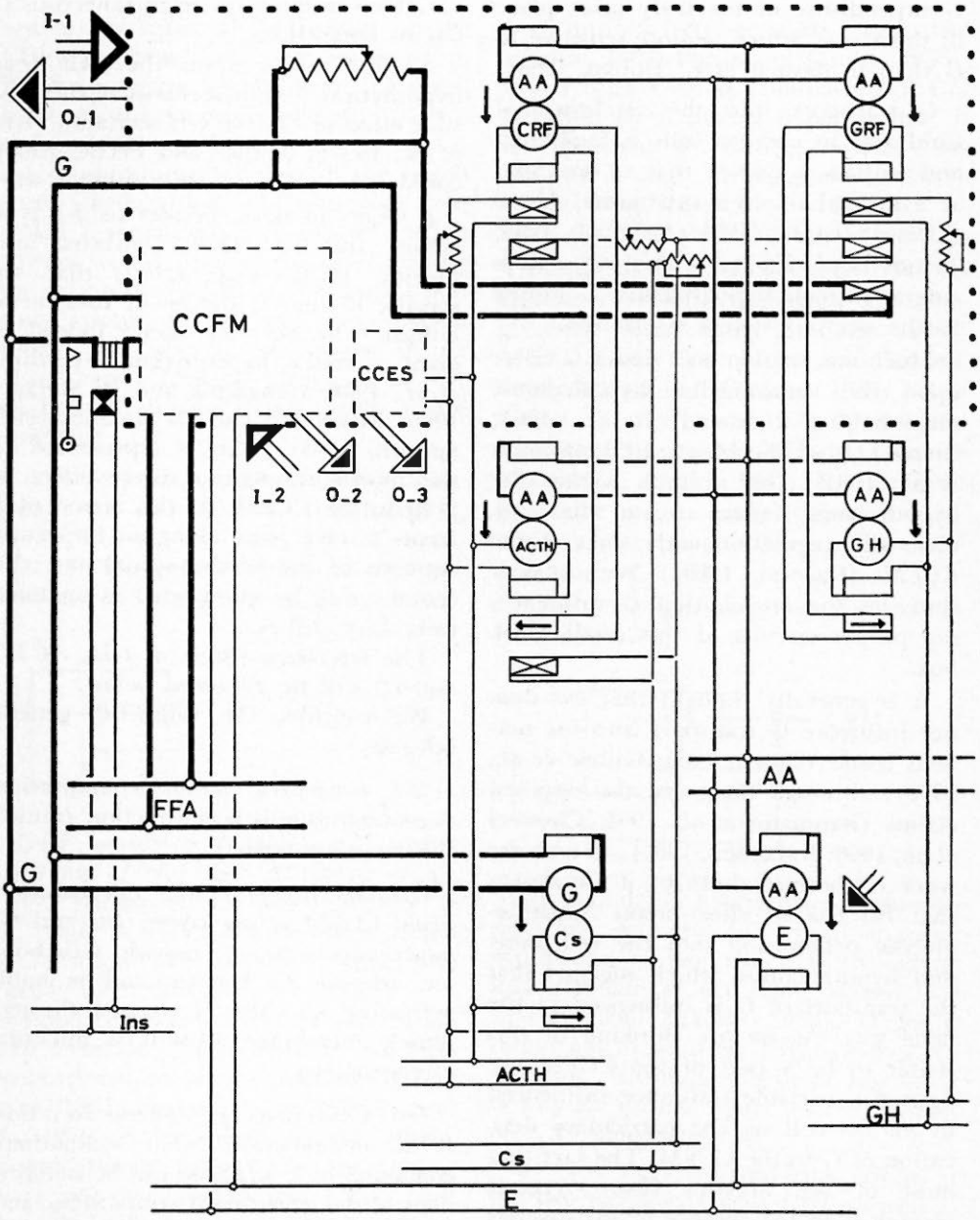


Figure 7. Model of the nervous system, the adenohypophysis and the adrenals. General circuits as in Fig. 2. Nervous black box delimited by dots. *CCFM*, center of control of fuel metabolism. *CCES*, center of control of epinephrine secretion. *I-1* arrow, unspecific afferentation; *I-2* arrow, specific interoceptive afferentation; *O-1*, arrow, unspecific (motor) efferentation; *O-2* arrow, specific vegetative efferentation; *O-3* arrow, control of epinephrine secretion (see text).

G expenditure of the body takes place in this tissue, which is more sensitive to *G* than to oxygen lack (Dolivo, 1966).

G transport into the cerebrospinal fluid and to nervous cells is facilitated and utilizes a carrier that is saturated at a normal or even sub-normal blood *G* level (Crone, 1965; Fishman, 1964; Joanny *et al.*, 1967). In this way, excepting in extreme hypoglycemia, *G* supply to the nervous system is ensured.

Much was written on a direct *G* effect upon the ventromedial hypothalamic glucoreceptors (Anand *et al.*, 1961; Anand *et al.*, 1964; Mayer, 1953; Oomura *et al.*, 1964). Our opinion is that the hypothalamic centers are, in what concerns this regulation, only links of the *CCFM* (Racotta, 1969). We consider thus, on the model, that *G* influences the proper circuits of this small black box.

It is generally thought that *Ins* does not influence *G* transport into the nervous tissue (Crone, 1965; Gilboe *et al.*, 1970), although there are also opposed claims (Baumann *et al.*, 1963; Chowers *et al.*, 1966; Rafaelsen, 1961). In a recent work (Debons *et al.*, 1970) it was shown that *Ins* has an effect upon Aurothioglucose penetration into the ventromedial hypothalamus, which suggests that the transport of *G* is influenced in the same way. As we are thinking of this center to be a part of the CCFM, we figured a variable resistance influenced by an *Ins* coil on the particulary derivation of *G* to the CCFM. The fact that most of the nervous tissue receives enough *G* in the absence of *Ins* suggests that *Ins*-dependence of the CCFM for *G* uptake represents a mechanism by which nervous system measures available *Ins* rather than glycemia.

G expenditure in the nervous system is represented in the model by a big variable resistance on an intranervous *G* circuit derivation.

A *FFA* action upon the CCFM is hypothetical, but it seems that the possible effect of *FFA* on *GH* secretion (Irie *et al.*, 1967*b*; Muller and Pecile, 1966) could take place in this indirect way.

E seems to have, besides its *I-1* type action (Bradley, 1960; Dewhurst and Marley, 1965), some effects that are specific to the regulation of fuel metabolism. The hormone seems indeed to elicit a reflex hyperglycemia (Ezdinli *et al.*, 1968; Gangarosa and Di Stefano, 1966; Rosenberg and Di Stefano, 1962; Sproull, 1963). This is represented in the model through a direct effect of *E* upon the CCFM. As this action of *E* seems to take place along an important segment of the cerebro-spinal axe, this center could be interpreted as anatomically very diffuse.

The feed-back effects of *GH*, *ACTH* and *Cs* will be discussed below.

We consider the following general outputs:

O-1. Unspecific (motor) efferentation. It commands muscle contraction (muscle *ATP* electromagnet).

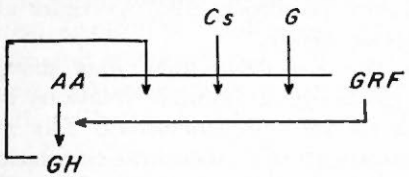
O-2. Specific vegetative efferentation. From CCFM acting upon: *Ins* and *Gg* pancreatic secretion; hepatic *Gln* booster; adipose *Tg* booster, and probably activating also the *G* passage through muscle membrane as well as muscular glycogenolysis.

O-3. Control of epinephrine secretion. It is demonstrated that sympathetic command of *E* secretion can be independent of the generalized sympathetic activation (Goldfien and Ganong, 1962; Schapiro, 1968), and it is for this reason that we figured a special nervous center on the model (CCES). This center should be considered to be under the continuous control of the remnant black box and also, more specifically in our

system, to suffer the influence of the CCFM. These last relations seem to involve a region beginning in the distal limit of the inferior colliculi (Cantú *et al.*, 1968), and extending as far as the thoraco-lumbar region of the spinal cord (Ikeda, 1968). The nervous controled *E* secretion which follows certain stresses would partially be produced by the action of *ACTH* on the central nervous system (Il'ina and Yanushkene, 1968), and not by the action of *Cs* (Linet and Hertting, 1966); it is why we figured an *ACTH* derivation acting upon the CCES.

O-4. Hypothalamic releasing factors. Only *GRF* and *CRF* are modeled (Fig. 7):

GRF. The general scheme of the conversion that are modeled is:



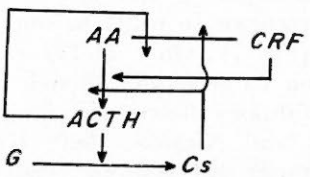
GRF existence is now well proven (Abrams *et al.*, 1966; Frohman *et al.*, 1968; Muller *et al.*, 1967; Schally *et al.*, 1966), as well as the feed-back action of *GH* upon *GRF* secretion (Muller and Pecile, 1966; Sawano *et al.*, 1967).

Blood *G* seems to exert an effect upon *GH* secretion, effect that is inversely proportional to *G* concentration (Earll *et al.*, 1967; Hunter *et al.*, 1966; Luft *et al.*, 1966; Rabkin and Frantz, 1966), though the relation could be neither strict nor very immediate. (Catt and Burger, 1968; Irie *et al.*, 1967*a*). Anyhow, this effect of *G* is at the hypothalamic and not at the hypophysial level (Abrams *et al.*, 1966; Katz *et al.*, 1967; Krulich and Mc Cann, 1966*b*; Reichlin, 1966). As to the eventual influence of *FFA* upon *GRF* secretion, it was discussed above (see *I-3*).

Cs inhibits *GRF* secretion (Frantz and Rabkin, 1964; Pecile and Muller, 1966). Concerning a direct stimulation of *GH* secretion by *E* during hypoglycemia, it is supported by rather indirect data (Blackard and Heidingsfelder, 1968) which come in conflict with other results (Luft *et al.*, 1966; Schalch, 1967).

Black box circuits command *GRF* secretion in various conditions, e.g. hypoglycemia (Krulich and Mc Cann, 1966*a*; Marks *et al.*, 1967; Meyer and Knobil, 1967; Rigal and Hunter, 1966), starvation (Marks *et al.*, 1965; Meites and Fiel, 1965), and muscular work (Hunter *et al.*, 1965; Schalch, 1967). It is believed that the reflex could be started by cellular glucopenia (Unger, 1965; Wegienka *et al.*, 1967).

CRF. The scheme of the conversions we modeled is:



Hypothalamic-hypophysial-adrenocortical axe is mobilized by all stressing conditions, among which is hypoglycemia (Donald *et al.*, 1968; Matsui and Plager, 1966; Zukoski, 1966). Hypoglycemia has an indirect effect upon *CRF* secretion (through the black box, that is why we do not figure a direct *G* coil on *CRF* generator).

Cs have negative feed-back effects at the two secretory levels: *CRF* as well as *ACTH* (Chowers *et al.*, 1967; Fleischer and Vale, 1968; Fortier, 1963; Slusher *et al.*, 1966). ACTH itself has a negative feed-back effect upon *CRF* secretion (Plager, 1967; Sawyer *et al.*, 1968). In addition, *Cs* as well as ACTH seem to have a series of unspecific central effects of the *I-1* type (Feldman and Davidson,

1966; Koranyi and Endroczi, 1967; Markov, 1964).

On all the mentioned feed-back circuits which are situated in the nervous black box we thought necessary to figure variable resistances that are under nervous control (Fig. 1*h*). This would account for the change in the set points of the different regulations produced during nervous reactions (e.g. stress).

G. *Adenohypophysis*

As it was already mentioned, only growth hormone and ACTH secretion are represented in the model (Fig. 7), and they were analyzed above in relation with their corresponding releasing factors.

H. *Adrenal cortex*

We modeled *G* and not cholesterol as *Cs* precursor in order to smplify the model (Fig. 7). Only *ACTH* is known to act on *Cs* secretion, though adrenal cortex histology shows a rich innervation (Shioda and Nishida, 1967; Unsicker, 1969; Yousef and Mahran, 1965) whose physiological rôle is uncertain (Spat and Sturcz, 1967). Animals are able to live quite normally with a transplanted gland (Childrees and Leeds, 1968).

I. *Adrenal medulla*

A motor-generator group representing $AA \rightarrow E$ conversion was modeled (Fig. 7). We did not consider necessary to figure norepinephrine secretion too, for the following reasons: a. *E* secretion is generally prevalent in mammals (Euler, 1963); b. Norepinephrine metabolic effects are similar, but usually less marked than those of *E*, at least in the actions considered in the studied system (Hagen and Hagen, 1964), and; c. If it seems to be proven that *E* could be secreted without a simultaneous norepinephrine secretion (Benedeczky *et al.*, 1965; Euler, 1963; Hökfelt, 1953; Schapiro, 1968), the reverse situation is less sure, at least in normal conditions (Goldfien and Ganong, 1962; Matsui, 1965).

E secretion is produced under nervous command in various conditions. *G* lack seems to be the only metabolic factor which influences (in a reflex manner) *E* secretion (Hagen and Hagen, 1964), but the degree of sensitivity of this reflex is controversial (Himsworth, 1968; Luft *et al.*, 1966). We did not found any data on an adrenomedullar mobilization during starvation. During muscular work, in some cases, there is a hypersecretion (Gollnick, 1967; Wright and Malaisse, 1968).

In the last years some data showed the existance of peculiar relations between *Cs* and catecholamines. The two hormonal groups, once into circulation, seem not to exert any reciprocal action upon their secretion (Goldfien and Ganong, 1962; Spat and Sturcz, 1967). However, in the adrenal gland itself, *Cs* seems to act on *E* synthesis (Coupland an Mac Dougall, 1966; Leach and Lipscomb, 1969; Roffi, 1968; Wurtman, 1966), and *E* seems to assure the integrity of the internal cortical zone (Brudieux and Delost, 1967). Moreover, cortical hormones could exert a potentiating effect on peripheral catecholamine actions (Brodie *et al.*, 1966). All these interrelations could be of importance for the hormonal balance of the whole organism, but do not, at a first look, seem to be essential for the functioning of the analyzed system.

DISCUSSION

The less that one could critically say concerning the model we present is that it is unfinished and that it may include some erroneous considerations. The latter is rather expected as our knowledge about the original system and many of its parts is incomplete and controversial. Some of the statements we made in the description of the model were full of doubts. But we think that the model is plastic enough to allow a lot of modifications which could improve it. There would be no difficulty, for example, to change the position of the glucocorticoid coil in adipose tissue, or to make the insulin hepatic coil to work, not on glucose 6-phosphate generator, but on a variable resistance which would regulate hepatic glucose input, and so on. Neither would it be troublesome to make insulin and glucocorticoid actions on the hepatic glycogen booster reciprocally interdependent, as some suppose they are.

The second critical point is much more serious: so far the model is only a blueprint, and nobody knows if it could really work as a physical device.

Cui prodest then this imperfect and unfinished model? We think, first, that it would be useful to set it up physically, either as it is planed, or through an analog computer. This does not deserve further argumentation: the modern biological litterature already showed the advantage of handling complex problems in this way.

However, we also think that the model could be useful even in its present form, and we shall discuss, in short, what it already achieved.

A. The modeling system (with DC electric devices) proved advantageous in this case, and could be successfully used in other biological models.

B. The sketch as such represents an excellent mnemotechnic device, which is understandable enough to grasp the details as well as the work of the whole system.

C. In designing the model we were lead to the general concept that the regulation of glycemia, which was initially the only system we attempted to model, is incomprehensible if one tries to consider it isolated from the more complex system it belongs to, that is to say, the regulation of fuel concentration. During its development, the model itself *requested* more and more data. There was a moment when the number of inputs exceeded the number of resolved relations, until finally these *requests* began to diminish, the circuits began to connect themselves, and the model was *self-satisfied* with the three physiological inputs. We came, in this way, to the conclusion that the logic of the model is close to the logic of the original biological system. If that is so, the model taught us that there is not a *glycemic regulation system*, but that glucose level represents possibly the most important but only *one* parameter of an *operational system of the biological fuels. One* of the rôles of this operational system would be to maintain the glycemic parameter above a minimal level and between certain limits, in all the situations it is programmed to cope with: rest, muscular work, starvation, etc.

D. Finally, the model has given some ideas upon certain mechanims which would be worthwhile to study more thoroughly. For example:

a. We encountered a *freack* –glycerol– whose blood concentration is very much influenced by the majority of the

other 12 circulating substances in the model but which, apparently, influences very few of them. Literature is very scanty in what concerns glycerol significance as an humoral regulatory factor. Is it really that glycerol has little importance in the system, or is our ignorance about its actions what make us think that way?

b. Some relations of tensions, qualitatively apparent in the model, could have great importance in the biological system. One of them we have already mentioned: the glucose 6-phosphate tension in the liver. Another could be the tension of liver glycogen, which most biologists think about as an *inert* material. However, there are some data (Brauss and Sasse, 1968) that glycogen concentration could regulate its own synthesis, a fact that our model shows implicitely. It was also suggested (Russek, 1971) that glycogen *tension* is monitored by hepatic receptors, and that this information participates in the regulation of glycemia and food-intake.

Such examples could be multiplied. We believe that other scientists would find matter for discussion, too. If the model could only suggest some important trends that are worth to aim at, its purpose would be well fulfilled.

ACKNOWLEDGEMENTS

We gratefully thank Dr. Mauricio Russek, from the Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional de México, for his friendly and invaluable assistance in revising the manuscript.

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