EXPERIMENTAL STUDIES ON THE PATHOLOGICAL
CHANGES IN THE SEVERAL ORGANS DUE TO
IRRITATION OF THE AUTONOMIC
NERVOUS SYSTEM

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CONCEPT OF REILLY'S PHENOMENA

Stimulation of the autonomic nervous system with various irritating agents
(either bacterial, toxic, chemical or physical) causes various lesions in various
organs in the body, mainly due to vasomotoric disorders. In other words, irri-
tation of the autonomic nervous system causes an unspecific type of symptom-
complex in the organism which is called “syndrome d’irritation neurovégéta-
tive” or “Reilly’s phenomena.”

The term “irritation” was first introduced by Claude Bernard, and was
later defined by Reilly as “such a stimulus as to cause a pathological lesions
in the body.” He emphasizes the difference between “irritation” and “excita-
tion” the latter being defined as “a stimulus which brings about a physiolog-
ical reaction in the body.”

It is well known that an excitation of the splanchnic nerve causes constrict-
tion of the vessels, whereas transection of the same nerve results in vascular
dilatation. However, when the splanchnic nerve receives an “excessive stimu-
lation” or an “irritation,” vascular surdilatation in a greater degree than when
the nerve is transected ensue. Dilatation of the vessels due to an irritation of
the splanchnic nerve is usually preceded by a transitory vascular constriction.
Therefore, it can be postulated that the vascular surdilatation is the result of
anoxia of the tissue.

Reilly’s phenomena manifest itself in various ways depending upon the
susceptibility or predisposition of individuals submitted to irritation.

Stimulating agents, even in a dose so small as to be usually quite innocu-
ous, may give irritation to the autonomic nerve when put in direct contact with the nerve and cause various lesions in various organs, not only in those organs which are under the direct control of the nerve, but also in remote organs. This long range effect of irritation is one of the characteristics of Reilly's phenomena and is the main subject of the study in our laboratory.

MATERIALS AND METHOD

Male guinea pigs weighing between 300 and 400 g, male rabbits around 2 kg of weight and male dogs weighing between 10 to 15 kg were used as experimental animals.

Twenty percent solution of alcohol, 1% solution of lead acetate or 3 to 5% aqueous suspension of peptone were used as chemical irritants. Under local anesthesia with 0.5% procaine hydrochloride, and through a median incision, autonomic nervous apparatus were exposed in the neck or abdomen, and one of these chemical agents (in an amount of 0.05 to 0.1 cc) was injected directly into the autonomic ganglia or into the nerve bundle. Faradic current from Du Bois Reymond's apparatus (2 Volts, 4 cm coil distance) was used as physical irritant and was delivered three times for 30 seconds each with 30 seconds interval. In the neck, irritation was given to the left sympathetic nerve bundle, or to the left parasympathetic nerve trunk at the level below the superior cervical autonomic ganglion. In the abdomen, left coeliac ganglia or left splanchnic nerve bundle was chosen as the site of irritation.

In the experiment on the lung, the technique of "sac jugulaire" as described below was used, too. The technique consists of putting two ligations to one of the jugular veins, thus forming a sort of balloon of the vein (sac jugulaire) and injecting the stimulant directly into the balloon, closing up the needle puncture with the third ligation. The chemical irritating agents seem to give a prolonged excitation to the vein endothelium.

Methods and adequate dose of the administration of some drugs utilized for the purpose of inhibition were as follows: Chlorpromazine was administered subcutaneously in an amount of 0.5 to 1 mg/kg for the rabbit and dog and of 1 to 3 mg/kg for the guinea pig, at 12 and 3 hours before the irritation and every 4 to 6 hours for the period of 24 to 48 hours after the irritation.

Cortisone was injected subcutaneously in an amount of 1 mg/kg of the body weight regardless of the species of the animal, every 12 hours starting from 24 hours prior to irritation to 48 hours after the irritation. ACTH was administered in a similar way as for Cortisone and in a dose of 1 I.U./kg of body weight regardless of the species of the animal.
RESULTS

Pancreatic Lesions

Following Laborit's recommendation on treatment of shock the authors have successfully treated a case of shock due to acute pancreatitis (which was proven by exploratory laparotomy) with a combination of Chlorpromazine and freezing.

In his theory about the pathogenesis of shock, Laborit emphasized the importance of the rôle played by dysfunction of the autonomic nervous system as well as that of the endocrine system and imbalance of body fluid.

Encouraged by clinical experiences of having successfully treated several cases of acute pancreatitis with the autonomic nerve blocking agent, the authors postulated that acute pancreatitis should be producible experimentally by giving a direct irritation to the autonomic nerve.

1) Experimental Production

The coeliac ganglia or left major splanchnic nerve of the dog and rabbit was irritated with chemical agent or with Faradic current. At three hours after irritation of the nerve, an elevation of serum amylase level above 256 Wohlgemuth's units, sometimes as high as 2048 Wohlgemuth's units, albuminuria, glucosuria, excretion of urobilin body in the urine and an increase in urinary amylase excretion were observed. On autopsy carried out between 24 and 48 hours after the irritation, pathological changes of acute hemorrhagic pancreatitis were seen in the pancreas (Fig. 1 and Fig. 2), and, in some of the cases, scattered hemorrhages in the lungs were demonstrated. Microscopic lesions were present in the liver and kidneys of all cases.

2) Influence of Some Drugs and Hypophysectomy

i) Inhibition by Chlorpromazine:—In those animals which were administered with Chlorpromazine in adequate dose, acute pancreatitis did not occur and serum amylase level and urinalysis were within normal limits at 4 hours after the irritation and autopsy at 64 hours after the irritation revealed no remarkable histopathological changes of pancreas. Chlorpromazine given in a larger doses (ten times as much as in the first group), however, seemed to facilitate the production of lesions.

ii) Inhibition by Hypophysectomy:—The pituitary gland was removed from the dog and then 7 to 10 days later, irritation with lead acetate was given to the autonomic nerve. Serum amylase level remained within normal limits, and in the histopathological finding pancreatic lesions were very slight.
The lesions in the adrenal, which will be discussed in detail later, were also mild. Pretreatment of the animal with a combination of hypophysectomy and adrenalectomy was also shown to prevent the occurrence of acute pancreatitis.

iii) Effect of ACTH and Cortisone:—ACTH was given to the rabbit in various amounts ranging from 0.5 units to 5 units. At 48 hours after irritation of the coeliac ganglia, aggravated lesions were observed in the pancreas and the adrenals in all of the animals thus treated. This result can be interpreted as showing the synergistic effect of nervous and humoral irritation. Cortisone in adequate dose, on the other hand, prevented elevation of serum amylase level as well as production of lesions in the pancreas and adrenal, but in a larger dose, it caused a marked elevation of serum amylase level, and did not prevent occurrence of lesions in the organs except in the adrenal gland.

3) Complications of Acute Pancreatitis

The various complications commonly accompanying acute pancreatitis are usually considered to be more or less coincidental or secondary pathological changes. However, in the author's opinion, taking the importance of Reilly's phenomena working as one of the factors in pathogenesis of acute pancreatitis into consideration, it seems quite natural for the other lesions to result from the same fundamental abnormality of the autonomic nervous system which initiate acute pancreatitis, and it seems that they only remain undetected because of their mildness.

**Gastric Lesions**

Increase in acidity of the gastric juice and exposure to various stressful conditions are two factors which are, by most of students, held most responsible for development of peptic ulcer. However, the exact mechanism by which "stress" causes peptic ulcer is poorly understood.

The authors performed on the guinea pigs the following experiments in order to clarify the rôle of the autonomic nervous system in the pathogenesis of peptic ulcer.

1) Experimental Production

i) When the vagal nerve trunk was transected in the neck, and an irritating agent was deposited on the end of either central or peripheral stump of the transected nerve, ulceration of gastric mucosa developed. When the cervical sympathetic nerve bundle was cut and irritation was given in the manner as in the experiment mentioned above, the result was as follows: When the irritation was given to the end of the peripheral stump, hemorrhage but not ulceration was produced in the gastric mucosa, whereas ulceration could be
produced by irritation of the end of the central stump of the nerve.

ii) In the experiment in which a small amount of alcohol or peptone solution was injected just around the vagal nerve in cardiac region of the stomach, pin-point hemorrhage, erosion or ulceration were observed to develop in the gastric mucosa of the greater curvature.

iii) Irritation with lead acetate injected into the left coeliac ganglia caused gastric hemorrhage, erosion or ulceration, which was enhanced to the extent of perforation by addition of 0.01 mg Neostigmine (Fig. 3 and Fig. 4).

iv) The experimental production of gastric ulceration by ligation of the pylorus in the rat was first reported by Shay in 1945. In the pathogenesis of the production of gastric ulceration in Shay’s rat, nervous factors, in our opinion, must be considered. In Shay’s procedure, the site of ligation has a great importance and if it is put a little more toward the duodenum, instead of on the pylorus itself, the ulceration did not occur. Shay has attributed this fact to contamination of gastric juice with duodenal content. However, the authors thought that there might be some particular factor in the site of the pylorus itself, and performed the following experiment in order to elucidate this factor.

In the guinea pig, 20% alcohol or 5% peptone was injected into the entire circumference of the pyloric wall. Five hours later, the stomach of the animal was inspected and found to show many petechial hemorrhage and ulceration. It is important to note that the guinea pig is the animal in which it is difficult to produce gastric ulceration by Shay’s procedure, but in which it is easy to produce various lesions due to Reilly’s phenomena. From the result of this experiment it seems reasonable to assume that the gastric ulceration produced by Shay’s procedure is actually due to irritation of the autonomic nerve in the pyloric wall and the lesion is one manifestation of Reilly’s phenomena.

2) Inhibition by Chlorpromazine

In the animal pretreated with Chlorpromazine in adequate dose, neither hemorrhage nor ulceration developed following irritation of the cervical autonomic nerve except when the peripheral stump of the transected vagal nerve was irritated. Cortisone administered in adequate dose likewise inhibited development of the lesions in the stomach.

Pulmonary Lesions

The authors have previously reported our clinical experience of a case of pulmonary infarction successfully treated by administration of Chlorpromazine. This experience has led us to undertake the following experiment in order to
clarify the rôle played by the autonomic nervous system in the pathogenesis of hemorrhage and edema of the lung.

1) Experimental production

Hemorrhagic lesions could be induced in the lung of the guinea pig by Faradisation of the cervical autonomic nerve or by the "sac jugulaire" method.

The pulmonary lesions appeared within a short period of time after irritation of the autonomic nerve, and varied in their severity from localized petechial and small scattered hemorrhage to large and extensive hemorrhage (Fig. 5). The petechial and small lesions were, however, observed to be gradually absorbed, and, at the end of 24 to 48 hours after the irritation, only larger hemorrhagic lesions were observed to remain as the chronic damage.

The smaller lesions were not detectable radiologically. The larger lesions, which were still present 7 days after the irritation, and were accompanied by parenchymal damage and histological reactions in the surrounding tissue, were demonstrable as the abnormal shadow in the X-ray film.

Histological study of the lesion revealed, in the early stage, capillary dilatation and congestion in the alveolar wall, and thickening of the alveolar septa. The lung was generally atelectatic and alveoli were collapsed. Alveolar spaces were filled with erythrocytes, giving the picture of so-called "pulmonary apoplexia." In some of the cases, there were also edematous changes in addition to the hemorrhage, but these lesions appeared somewhat different from those seen in other organs (Fig. 6). The finding seems to offer a basis for explaining pathogenesis of pulmonary edema seen in clinical cases. These pictures of vascular disturbance were observed to be absorbed and mostly disappear in the course of time, but a part of them became accompanied by parenchymal damage and local tissue reactions, giving the picture of so-called incomplete infarction or infarction-like lesion, or, in some of the cases, that of pneumonia (Fig. 7 and Fig. 8).

2) Effect of Chlorpromazine, Cortisone and ACTH

These lesions were inhibited by either Chlorpromazine in doses from 1 to 2 mg/kg or Cortisone in adequate dose. Administration of ACTH, on the other hand, resulted in aggravation of these lesions.

Adrenal Lesions

During the course of the above experimental studies the finding came to our attention that various lesions were almost invariably observed in the adrenal glands of animals exposed to irritations, wherever the site of irritation may be. This finding induced us to postulate a direct influence of the autonomic
nervous function upon that of the adrenal cortex.

The authors performed the following experiments and investigated autonomic nervous control of adrenocortical function.

1) Experimental Production

i) When a stimulating agent was put in contact with the cervical or abdominal autonomic nerve, hemorrhagic lesions and degeneration were always seen to occur in the adrenal of both sides which involved extensively all the part of the organ (Fig. 9). In the experiment in which the autonomic nerve was transected and Faradisation was applied to the end of the nerve-stump, the irritation to the end of the peripheral stump induced more extensive hemorrhage in the adrenal than that to the end of the central stump, regardless whether the transected nerve was sympathetic or parasympathetic.

ii) Histopathological changes in the adrenal: Irritating the left splanchnic nerve by Faradic current, it was revealed that intense hemorrhage, degeneration and necrosis took place in the left adrenal gland in the first one hour and these were aggravated more and more in the following several hours (Fig. 10). In the right adrenal gland, however, only the slight prenchymatous lesions appeared.

2) Effect of Chlorpromazine, Cortisone and ACTH

Chlorpromazine, Cortisone administered in an adequate dose respectively protected the adrenal from the noxious influence of the irritation to autonomic nerve, whereas Chlorpromazine, Cortisone or ACTH in a dose ten times as much caused the adrenal glands to suffer more extensive lesions under the influence of the same irritation.

3) Difference between the Left and Right Adrenocortical Reaction after the Irritation of the Left Splanchnic Nerve Bundle

After the irritation of the left splanchnic nerve bundle by Faradic current the difference in content of ascorbic acid between in the left and right adrenal glands occurred apparently one hour later. It was found after several hours, however, that the ascorbic acid was depleted in both adrenal glands and the difference almost disappeared.

4) Influence of Autonomic Nervous Irritation in the Hypophysectomized Dog

The dog was firstly hypophysectomized, and, one month later, one of its adrenals was removed. Histologically the removed adrenal showed normal glomerulosa zone, degeneration and decrease in number of the cells in fasciculata and reticularis zones (Fig. 11). The coeliac ganglia of the hypophysectomized-semiadrenalectomized dog was irritated and the remaining adrenal was examined histologically 4 hours later and it seemed to be activated by the
nervous stimulation (Fig. 12). The content of ascorbic acid in the left and the right adrenal glands of hypophysectomized dogs were apparently different after the left splanchnic irritation.

The findings of these experimental study seemed to suggest that irritation of the autonomic nervous system initiated lesions in the adrenals giving rise to a disturbance of the whole endocrine system, the latter in turn, causing the adrenals to suffer from aggravation of the lesions, and that the adrenal function also was stimulated by the autonomic nervous irritation.

SUMMARY

1. Various lesions were produced in the pancreas, stomach, lungs and adrenals by giving nervous irritation directly to the cervical autonomic nerves, coeliac autonomic ganglia or the splanchnic nerve.

2. Production of these lesions were prevented or ameliorated by administration of Chlorpromazine or Cortisone in adequate doses or by hypophysectomy, whereas administration of these agents in larger doses, or of ACTH aggravated these lesions.

3. These experimental results were interpreted as indicating that irritation given to the organism induces various lesions in various organs through a direct pathway of peripheral autonomic nerves, as well as through that of peripheral autonomic nerve-diencephalon-pituitary-adrenal axis. In other words, both the autonomic nervous system and pituitary adrenal axis are participating cooperatively with each other, in the pathogenesis of Reilly's phenomena as well as in that of Selye's general adaptation syndrome. Finally, the authors wish to stress that these two unspecific phenomena must be summarized and organized theoretically in a category of "agressology."

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REFERENCES

Fig. 1 Hemorrhage and degeneration and necrosis of pancreas produced by nervous irritation by 1% lead acetate on the coeliac ganglia. Rabbit, H. E. ×80
Fig. 2 High-power view of a portion of degeneration of pancreas by 3% peptone. Rabbit, H. E. ×320
Fig. 3 Perforated gastric ulcer following irritating coeliac ganglia with 1% lead acetate, combined with 2 times subcutaneous injections of 0.01 mg Neostigmine. Guinea pig.
Fig. 4 Microscopical picture of a perforated portion of Fig. 3. H. E. ×50
Fig. 5 Severe hemorrhage of the lung produced within 3 hours after irritation of the cervical autonomic nerve. Guinea pig.
Fig. 6 Engorgement of blood vessels, hemorrhage into alveolar spaces and collapse of alveoli in the lung within 3 hours after irritation of the cervical autonomic nerve. H. E. ×320
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Fig. 7 Hemorrhage, edema, engorgement of blood vessels and necrosis of alveolar wall of the lung, at 48 to 72 hours after irritation of the cervical autonomic nerve. H. E. ×320
Fig. 8 Hemorrhage and cellular infiltration in the lung, at 48 to 72 hours after irritation of the cervical autonomic nerve. H. E. ×150
Fig. 9 Atrophia and degeneration of adrenal cortex produced by Faradisation of the left cervical vagus. Guinea pig. H. E. ×80
Fig. 10 Hemorrhage and degeneration of the left adrenal cortex on the third hour after Faradisation of the left splanchnic nerve. Guinea pig. H. E. ×150
Fig. 11 Atrophy of cortical cells one month after the hypophysectomy. Dog. H. E. ×80
Fig. 12 Hypertrophy of cortical cells after Faradisation of the right splanchnic nerve. Hypophysectomized dog. H. E. ×80