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Hämorrhagische Reaktionen
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Hemorrhagic Reactions[1]

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From the time of its discovery up to date, the phenomenon of local tissue reactivity has confronted us with certain characteristics which made us speculate whether it represents an experimental pattern for the production of a variety of diseases of obscure etiology and certain syndromes complicating diseases of known etiologies. I for one have always been impressed by the non-specificity of the phenomenon in the strict immunological sense, since it represented a new concept at a time when great emphasis was being laid upon specific reactions to specific causes. When search for new specific etiological agents came to a deadlock, there was an opportune moment to pay greater attention to the reactions of the host, to determine whether there exist mechanisms which may call forth synergistic action of multiple causative agents resulting in specific reactions to non-specific causes. Thinking along these lines was greatly aided by the demonstration of a characteristic pathological damage, namely, striking hemorrhagic necrosis in response to a variety of bacterial toxins, antigen-antibody complexes, and certain colloidal agents, in sites prepared by bacterial toxins. We had before us a characteristic, well defined type of pathological lesion which could be obtained by substances remote from one another in chemical structure and yet in spite of their non-specificity grouped in such a manner as to explain the clinically well known interactions of bacterial sensitizations with non-bacterial allergies, and a great variety of complications of bacterial and viral diseases by supervening secondary invaders and toxic agents. Vascular participation was the paramount basic principle underlying these reactions pointing out the profound pathological changes which may take place through the presence of toxic agents in the blood stream

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of a host when tissues have been made reactive by local influences. The importance of this principle was brought out emphatically by the histology of the lesion and unequivocally supported by one essential prerequisite for the production of the phenomenon—the necessity to introduce the provocative agent into the vascular system, suggesting the participation not only of the vascular system but also other important systematic functions of the organism. These two phases of the phenomenon, the histology of the lesion and the participation of the vascular system in the phenomenon will be the main subject of my presentation, thus dealing with the events concerned with the provocation of the phenomenon. For lack of time I shall leave out completely consideration of the mechanisms involved in the elicitation of the state of reactivity following the preparatory injection.

In reviewing the phenomenon two modes of its production have to be kept in mind, the local phenomenon resulting from a local preparation followed by an intravenous injection, and the general phenomenon resulting from two intravenous injections, twenty-four hours apart.

In the general phenomenon, the kidney lesions are predominant, occuring only irregularly in other organs. There is characteristic necrosis of the glomeruli, the convoluted tubules, and the intralobular arteries. Many glomerular capillaries are filled with conglutinated red blood cells. The necrotic tissue is divided into small areas by zones of infiltrating polymorpho-nuclear leucocytes. These areas are not necessarily separated by intravenous segments of preserved kidney. Indeed, necrosis may extend almost uninterruptedly over the entire cortex, the older areas, joined by fresher zones of destroyed renal tissue. The arcuate arteries and their larger branches are free from thrombi. The walls of the interlobular arteries and the afferent arteries are necrotic. Conglutination thrombi are seen in glomerular loops and cortical interstices.

Thus, there is a striking similarity between experimental and human renal cortical necrosis, namely, symmetry and extent of the lesion; localization in the cortex; restriction of necrosis to arteries of the smallest order, 150 μ or less, with lack of lesions in arcuate and larger arteries; the appearance of thrombi, which are composed of platelets and fibrin enmeshing red and white cells; and finally, the fact that lesions in the general phenomenon as in the human syndrome of renal cortical necrosis are predominantly renal and occur only irregularly in other organs. Since the primary disturbance is circulatory, as attested by distribution of lesions which always spares the medullary and subcapsular layers, a redistribution of renal circulation appears possible. The concept may be formulated on the basis of the interesting studies of *Trueta*. The author

demonstrated in rabbits a dual circulation of the kidney under the control of the autonomic nervous system. A reflex renal artery spasm has been shown following limb injury, stimulation of afferent sciatic nerve fibers, efferent splanchnic nerve fibers, large doses of epinephrine, pitressin or staphylococcus toxin. The distribution of bilateral renal cortical necrosis can be then explained on the basis of interlobular artery constriction within the cortex, while the medulla which remains viable is supplied by the lesser circulatory route.

Thus, as I said repeatedly, in the local and the general phenomena we clearly recognize the role of the vascular system. It yet remains to determine what particular set of events takes place when the provocative agent is introduced into the circulation. A clearer approach to the problem may be obtained by examination of the following long list of various substances tested for their effect upon the phenomenon with negative results, namely, acetylcholine, adenosine-5-phosphoric acid, alypin, antiplatelet serum, amino acids in various combinations, ascorbic acid, atropine, benadryl, biotin, calcium chloride, calcium gluconate, casein hydrolysate, choline, cocaine, congo red, curare, DCA, dicumarol, distilled water, estradiol, ether general anesthesia, folic acid, glucose, heparin, hesperidin, histaminase, histamine, india ink, inositol, lemon «citrin», milk, Niagara sky blue, nicotinic acid, pantothenic acid, paraminobenzoic acid, physostigmine hydrochloride, pilocarpine, progesterone, pyribenzamine, pyridine in doses reducing significantly the blood platelet count, pyridoxal, pyridoxamine, pyridoxine, rat liver extract, rat spleen extract, riboflavin, sodium oxalate, sulfadiazine, sulfanilamine, sulfathiazole, thiamine, a-tocopherol, toluidine blue, trypan blue, trypsin, urethane, vitamin K water-soluble and oil-soluble preparations, wheat germ oil, yeast extract, BAL, mapharsen, partial exsanguination, thyroidectomy, and anthisan.

The negative effects of the substances mentioned above exclude several mechanisms:

The possibility that a disturbance in the coagulation system is necessary for the elicitation of the reaction is not supported by the fact that agents capable of altering blood coagulation, namely, distilled water, heparin, dicumarol, vitamin K, calcium salts, sodium oxalate, pyridine and anti-platelet serum fail to produce any effect upon the phenomenon. The role of the peripheral and central nervous system in the provocation of the phenomenon is excluded by lack of effect of general anesthesia and a variety of local anesthetics, atropine, acetylcholine, physostigmine, curare and pilocarpine. The suggestion that the reaction may be caused by release of histamine following the provocative injection is not borne

out by the inability of histamine to provoke the reaction and failure of histaminase and anti-histaminics to exert any consistent influence. Assumption receiving most support was that the damage to vascular endothelium necessary for the production of the reaction can be elicited only when the provocative agent is brought in contact with the endothelium intravascularly. *Becker* recently showed that nitrogen mustard, benzol and X-ray radiation are capable of suppressing the phenomenon. He postulated that these agents, all having one feature in common, namely, their effect upon the reticulo-endothelial system produce the suppression by rendering the vascular endothelium anergic in the prepared site, thus preventing it from reacting to the provocative agent. These endothelial cells being rendered anergic are not able to react to the active principles in a way that otherwise would be self-distructive.

Although these observations are readily confirmed, there are some investigations which contradict the assumption that the substances studied produce their effect by rendering the endothelial cells of the prepared sites anergic. In studying the mechanism of this action, *Schlang* found that protection of the prepared site from the effect of nitrogen mustard failed to influence the inhibition of the phenomenon. In contrast, protection of the lower limbs from the action of nitrogen mustard by aortic occlusion decreased or prevented the inhibition. He justly concluded that the effect of nitrogen mustard was the result of systemic rather than local action. Histological changes in the bone marrow and hematological examination of the peripheral blood after administration of nitrogen mustard suggested that the marrow played a role in the decreased inhibition seen after aortic occlusion. That the suppression of the activity of the reticulo-endothelial system may play an opposite effect is brought out by experiments of *Beeson*. A study was made by him on the effect of reticulo-endothelial blockade upon natural or induced immunity of rabbits to the phenomenon. When thorotrast was used as the blocking agent, rabbits previously immune to the phenomenon responded after the injection of thorotrast by developing typical areas of hemorrhagic necrosis. The conclusion was that the function of the reticulo-endothelial system was necessary for immunity, while its suppression enhanced the susceptibility to the phenomenon. Although it is realized that the diametrically opposed results of *Becker* and *Beeson* may have been due to the use of different agents for suppression of the reticulo-endothelial system, the experiments of *Schlang* just quoted lead to the conclusion that the function of the reticulo-endothelial system as important as it may be, cannot be the sole factor in the provocation and suppression of the phenomenon. In pertinent studies, *Stetson* in the U.S.A.

and *Hoigné*, *Koller* and *Storck* in Switzerland found that a profound thrombocytopenia, granulocytopenia and increase in antithrombin concentration occur during the second stage of the phenomenon, prior to the actual onset of hemorrhage in the prepared skin sites. These hematological alterations appear to be due to accumulation of the cells mentioned in the capillary bed of the lungs and perhaps other internal organs. This seems to be consequent on certain changes in the platelets and polymorphonuclear leucocytes which result in the formation of clumps of these elements. In skin areas prepared for the phenomenon and rendered sensitized through a mechanism still obscure, the capillaries and small veins exhibit an extraordinary vulnerability to occlusion by aggregates of platelets and granulocytes which takes place after the provocative injection. The resulting interruption of the blood supply is followed or occurs incidentally with death and disintegration of many of the involved vessels of the cells of the adjacent inflammatory exudate. Bleeding into the tissues completes the alterations characteristic of the phenomenon. Thus, on examination of the facts available, it cannot be doubted that the mechanism of provocation of the phenomenon involves the participation of many important systemic functions.

There will be no time to review the direct and indirect experimental and clinical evidences accumulated over a period of some twenty years, that the phenomenon under discussion demonstrates the mechanism underlying the production of a variety of spontaneous diseases and syndromes of known and unknown etiologies in which vascular lesions are a predominant feature and complications of bacteremias and toxemias with hemorrhagic diathesis. Following the introduction of ACTH and cortisone, it was of course of great interest to note that these hormones proved therapeutically efficacious in some of the diseases in which the phenomenon was assumed to represent the underlying mechanism. The correlation obviously led to the examination of the effect of ACTH and cortisone upon the phenomenon. In these studies the substances under investigation were injected intramuscularly at various intervals of time preceding the preparatory and provocative injections of meningococcus culture filtrate. The amounts of the filtrate used contained at least 50 minimal phenomenon-eliciting units.

Thus, as may be seen from table 1, ACTH did not influence the phenomenon when injected prior to the preparatory injection. However, the administration of a sufficient dose of the hormone (12.5 mg per animal) preceding the provocative injection completely suppressed the phenomenon in 8 out of 10 animals tested. Smaller doses of ACTH similarly injected produced only irregular inhibition. The results may be considered

Table 1

Preparatory treatment			Preprovocative treatment			Reactions		
Substance	Dose	Hr prior to I.D. inj.[2] of bacterial filtrate	Substance[1]	Dose	Hr prior to I.V. inj.[3] of bacterial filtrate	Strongly positive	Doubtful	Negative
—	—	—	—	—	—	26	0	2
—	—	—	PS	0,5 oxytocic u. + 0,5 pressor u.	2	4	0	1
—	—	—	PS	0,75 oxytocic u. + 0,75 pressor u.	1	5	0	0
—	—	—	PS	0,75 oxytocic u. + 0,75 pressor u.	2	6	0	0
ACTH	2 × 5 mg	18 and 1	—	—	—	4	0	0
ACTH	12,5 mg	2	—	—		6	o	o
—	—	—	ACTH	2,5 mg	2	1	0	1
—	—	—	ACTH	5 mg	2	2	3	1
—	—	—	ACTH	2 × 5 mg	18 and 1	1	2	1
—	—	—	ACTH	12,5 mg	2	2	0	8

[1] PS = Pituitrin-S, Parke Davis & Co., 1 ml containing 20 oxytocic units and 20 pressor units. ACTH = Adrenocorticotropic hormone, batch H3706, 12,5 mg containing 0,5 oxytocic units and 0,375 pressor units.
[2] I.D. inj. = Intradermal injection. [3] I.V. inj. = Intravenous injection.

highly significant if contrasted with the high incidence of reactions obtained in the control groups. It is also obvious that the suppression of the phenomenon could not be attributed to the presence as contaminants of oxytocic and pressor substances in the ACTH solutions, since surgical pituitrin containing larger amounts of these substances than those present in ACTH solutions failed to produce the effect. In later studies it was found that the optimum time for obtaining inhibition of the phenomenon with ACTH injected intramuscularly or intravenously was about 2 hours preceding the provocative injection of the toxin. This period of time is approximately the time necessary to produce maximum mobilization of the adrenals by ACTH. It was of interest that ACTH was capable of protecting the tissues from damage by agents to which they were sensitive without removing the state of sensitization. This effect is similar to clinical therapeutic results in which ACTH suppresses manifestations of diseases without removing their cause. The experiments clearly established a definite relation between adrenocortical function and provocation of the phenomenon, indicating the possible regulatory

mechanism of the adrenal cortex in the production of the phenomenon. It may be further assumed that the production of the phenomenon in turn depends on a profound systematic disturbance leading to immobilization of this regulatory protective role of adrenocortical function. This immobilization brings about a series of disturbances involving apparently many systematic functions. When viewed in this light it becomes possible to understand why no one single structural system could be considered solely responsible for the provocation or suppression of the phenomenon in previous studies.

Consistent with these findings are the observations of other authors that ACTH diminishes human skin reactions of bacterial hypersensitivity of the delayed type without affecting histamine reactions and reactions of the immediate type. The hormone does not interfere with antigen-antibody reactions, but alters the capacity of the host's tissue to respond to certain types of toxic agents.

About the time the studies on the effect of ACTH on the phenomenon of local tissue reactivity were completed, *Smith* and *Humphrey* in England reported that sodium salicylate was capable of suppressing the phenomenon elicited with E coli toxin. In some rabbits the reaction was completely inhibited, while in others the size of the reaction was markedly reduced. The authors related this effect to the stabilizing effect of sodium salicylate upon capillary permeability, previously described by *Swyer*. However, when examined from the point of view of the results obtained with ACTH, it seemed plausible to me to assume that the inhibition of the phenomenon may be due to ACTH-like activity of sodium salicylate. About the same time and shortly afterwards experiments were published which brought ample support to this assumption. *Marshall* et al. demonstrated a fall in adrenal ascorbic acid following administration of sodium salicylate, while there was little change in hypophysectomized rats. Later *Pasqualini* and *Garberi* found that the effect of sodium salicylate upon adrenal ascorbic acid level was much more pronounced and sustained than that produced by adrenaline. A beautiful illustration of the ACTH-like effect of aspirin is offered by the case described by *Cochran* and *Reid*. A child given massive doses of aspirin for treatment of rheumatic fever developed mild but definite symptoms of *Cushing*'s syndrome, diminished glucose tolerance, glucosuria, water and chloride retention, and a negative nitrigen balance, all manifestations being indicative of hyperfunction of the adrenal cortex.

On repeating the experiments of *Smith* and *Humphrey* using a stronger toxin (meningococcus) we found that the phenomenon could be completely inhibited in about 60% of rabbits, while in the remaining rabbits

the reactions were strongly positive. The size of the reactions was not reduced. In interpreting the results as due to ACTH-like activity of sodium salicylate it occured to us that the variability in the results may be due to the individual differences in the ability of the adrenal cortex to respond to this stimulation. Our attention turned then to pantothenic acid. It is known that pantothenic acid deficiency produces adrenocortical damage and dysfunction. According to *Gaunt, Liling* and *Mushet*, rats on a diet deficient in pantothenic acid show a decreased resistance to water intoxication. As stated by *Williams* it is highly suggestive that pantothenic acid may play an important role in certain phases of synthesis of steroids by the adrenal cortex. It was of interest, therefore, to determine the effect of combined treatment of rabbits with sodium salicylate and pantothenic acid upon the phenomenon.

Table 2

Treatment			Results		
Substance	Total dose	Method of administration	Pos.	Doubtful	Neg.
Sodium salicylate	1,6 g/kg	I.P. 20 min. prior prep. inj. 18 h, ½ h prior prov. inj. and 2 h after prov. inj.	12	0	17
Calcium pantothenate . .	0,8 g/kg	idem	6	0	0
Sodium salicylate and Calcium panthotenate .	1,6 g/kg 0,8 g/kg	idem	0	1	5
Sodium salicylate and Calcium pantothenate .	1,6 g/kg 0,4 g/kg	idem	0	0	10
Sodium salicylate and Calcium pantothenate .	1,6 g/kg 0,2 g/kg	idem	2	0	4
Controls			65	3	3

As may be seen from table 2, a massive dose of sodium salicylate suppressed the phenomenon in 17 out of 29 rabbits. Calcium pantothenate alone in a large dose failed to produce any effect. However, administration of sodium salicylate in combination with calcium pantothenate resulted in complete inhibition of the phenomenon in all animals tested. Thus, calcium pantothenate enhanced the suppressing effect of sodium salicylate without directly affecting the phenomenon. Similar experiments were carried out with aspirin administered orally and calcium pantothenate intraperitoneally. The results were analogous, aspirin alone producing inhibition of the phenomenon in about 50% of rabbits and the combination of aspirin and calcium pantothenate giving a considerably higher rate of protection against the phenomenon. By

contrast, the effect of adrenaline administered in large doses proved equivocal, calcium pantothenate having a doubtful adjuvant action. It seems, therefore, reasonable to assume that the ability of the drugs studied to suppress the phenomenon follows closely their ACTH-like activity. It will be recalled that sodium salicylate produces a sustained and prolonged drop in adrenal ascorbic acid, while adrenaline gives only a slight decrease for a short period of time.

The complementary role of calcium pantothenate is of particular interest. It is suggestive that in time of stress the adrenal cortex may not be able to produce an adequate quantity of hormones, not because of its limited functional ability but through lack of a sufficient amount of building materials in a normal economy. By making an ample supply of these materials available the adrenal cortex properly stimulated may be able to meet the emergency requirements for rapid synthesis and an unusually large output. A series of investigations along these lines suggest themselves.

I have limited myself thus far to the consideration of ACTH and ACTH-like substances having left the examination of cortisone to the last in view of its distinctly different behaviour. In studies on the effect of this substance upon the phenomenon, extremely large amounts were required to produce a suppression of the phenomenon, namely, doses 6 times greater than those of ACTH. The difference between the effects of ACTH and cortisone is also apparent from studies of *Thomas* concerned with the bilateral renal cortical necrosis. It will be remembered that the production of this lesion required two intravenous injections of bacterial toxin 24 hours apart, the incidence being about 25% in a large number of rabbits tested by various authors and myself. *Black-Schaeffer* obtained a high incidence of lesions following repeated injections of live meningococcus cultures. Single injections of live bacteria or bacterial toxins failed consistently to produce this lesion. It is for this reason that the lesion has always been considered in the literature as the generalized *Shwartzman* phenomenon. *Thomas* treated rabbits with 25 mg of cortisone daily for 4 days and gave a single injection of meningococcus toxin on the third day of cortisone injection. Adequate control groups of rabbits injected with cortisone alone, and rabbits receiving a single injection of toxin alone, accompanied this experiment. Bilateral renal cortical necrosis was seen in a high percentage of cortisone-treated rabbits 24 and 72 hours following a single injection of toxin. The lesions were very severe, confined to the cortex and sharply demarcated from the medulla. Microscopically, there was marked tubular necrosis, interstitial hemorrhages and numerous thrombi in the glomeruli. In this

connection it is highly pertinent to recall a paper by *Apitz*, published in 1935, in which he reported that occasionally a single injection of toxin produced bilateral renal cortical necrosis in pregnant rabbits. We know now that there is a greatly enhanced production of cortisone in pregnancy. The experiments thus offer an explanation for the comparatively high frequency of bilateral renal cortical necrosis under conditions of stress, hemorrhage in particular, in pregnant women. Obviously, under such conditions the already increased production of cortisone in pregnancy may be expected to be still further enhanced, thus creating optimum conditions for production of renal cortical necrosis with the aid of some intervening toxin. There is ample and fast accumulating evidence that cortisone produces enhancement of infections. I for one reported last winter that cortisone elicits an extraordinary enhancement of susceptibility to poliomyelitis infection. Mention is merely made in order to point out that in my studies on poliomyelitis, it was noted that while cortisone produced a dramatic enhancing effect, ACTH failed to modify the normal susceptibility of the animal. In the experiments by *Rich* concerned with the production of nephritis and periarteritis nodosa by chronic protein sensitization of rabbits, there was also observed an important difference in the effect of ACTH and cortisone. Both ACTH and cortisone depressed the proliferative glomerular lesions, but whereas ACTH maintained the glomeruli in a normal state, treatment with cortisone induced the development of a quite different type of severe glomerular damage with accentuated hemorrhage which has its counterpart in human acute hemorrhagic glomerulo-nephritis.

Thus, the experiments on the phenomenon of local tissue reactivity as well as those on infections and some types of protein sensitization point to a marked difference in the behaviour of cortisone and ACTH. Until now, in view of the similarity in clinical therapeutic results little allowance has been made for possible differences between physiological effects of ACTH and cortisone. It is widely believed that the major role of adrenal cortex is to render the body generally more resistant to injury from a variety of causes and maintain a normal function of the cells of the body. ACTH stimulates the adrenal cortex as a whole, thus probably eliciting also the production of other adrenocortical hormones in addition to cortisone (or compound F) in intricately equilibrated quantitative relationships. Moreover, the stimulated adrenal cortex causes a variety of responses in other endocrines. In sharp contrast, the administration of cortisone or hypersecretion of cortisone by the adrenal cortex in abnormal states results in a series of metabolic events set into a single direction depressing temporarily other functions of the adrenal cortex.

The outcome is then a greater imbalance, and a more significant lack of control of the physiological capabilities of cortisone than following ACTH administration. These considerations may well serve for the understanding of differences in behaviour of ACTH and cortisone, insofar as problems of infection and resistance are concerned. They may also offer a basis for studies on possible controlling and antagonistic effects of other hormones.

There are, however, certain experimental observations in which no difference between the effects of ACTH and cortisone could be detected, those concerned in particular with the reactions of the eye. *Woods* and *Wood* found that both agents injected parenterally have a profound effect on the inflammatory phase of the hypersensitive reaction, blocking the inflammation and exudation which occurs in the ocular protein anaphylactic reaction, the ophthalmic reaction secondary to bacterial allergy, the focal reaction in tuberculous eyes, and inflammatory reactions produced by various irritants.

Thus it appears that whether ACTH and cortisone will act similarly or dissimilarly may depend on many factors, namely, type of tissue involved, type of lesion, nature of the injurious or infectious agent and the underlying mechanism of production of injury.

It seems that the more we discover, the more there is left to discover. We are now about to enter a vast and as yet unexplored field of relation of infection and resistance to endocrine function. New observations show a close conditioning at least by certain endocrine factors of pathogenesis and predisposition to toxic and infectious processes. No doubt the studies go as far as to teach us a lesson that any evaluation and characterization of the action of a toxic or infectious agent must be continuously considered side by side with the complex physiological mechanisms governing the response of the host.