1951

Immunological and anaphylactoid responses as modified by adrenal cortical stimulation

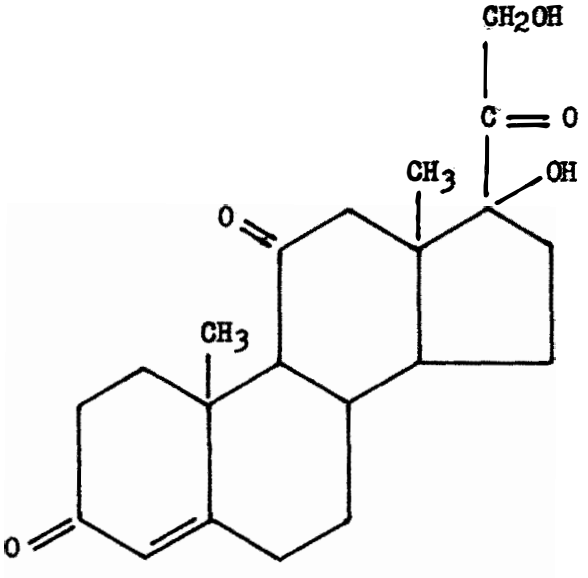
Richard A. Pettee
University of Nebraska Medical Center

IMMUNOLOGICAL AND ANAPHALACTOID RESPONSES AS MODIFIED BY ADRENAL CORTICAL STIMULATION

Richard A. Pettee

Senior Thesis

Presented to the College of Medicine
University of Nebraska
Omaha - 1951



Cortisone, Compound E

11 dehydro 17 hydroxycorticosterone

Introduction

Considerable evidence has been accumulated to indicate that the endocrine gland system plays an important role in the response of the body to a wide variety of physical, chemical, and microbic stresses. It has long been known that people with Addisons Disease are particularly vulnerable to relatively innocuous infections.[10] The nonspecific reaction pattern (anamnestic response) seems impaired in those with symptoms of Addisons Disease or pituitary cachexia.[18] Also, people with Addisons Disease do not develop such reactive or allergic disease entities as arthritis, gout, or psoriasis.[29]

The anamnestic response has been produced by intramuscular injection of whole blood, foreign protein (fever therapy), x-ray, inanition, epinephron, heat and cold. All these early works attempted to relate the concomitant fall in lymphocytes and the rise in neutrophiles to the specific stimulus acting upon the adrenal cortex. Fortier[11] reports as a response to these stresses enlargement of the adrenals and a decrease in cholesterol and ascorbic acid, probably precursors of 11 dehydro 17 hydroxycorticosterone. Selye[26] by his theory of adaptation, showed that all these stimuli produce a non-specific reaction psttern, resistance being produced through excess secretion of ACTH (adrenocorticotropic hormone) of the anterior pituitary. Selye has gone on to divide the hormones of the adrenal cortex into two large groups, one, the mineral corticoids, represented by desoxycorticosterone. The other group is referred to as glucocorticoids which have a cortisone-like action.

There have been varying reports on the literature for over a decade concerning the beneficial therapeutic effects of adrenal cortical extracts on such things as pimphigus.[30] These early investigative attempts were, however, very inconsistant and difficult to reproduce. This was so largely because only relatively small amounts of unknown potency were obtainable, and there was no attempt to separate the various adrenal cortical steroids produced by the gland.

Prior to the discovery by Hench and co-workers[15] on the beneficial effects of ACTH on rheumatoid arthritis, work was largely limited to its direct metabolic effects. After the spectacular response shown by rheumatoid arthritis to ACTH, a disease of reactivity and hypersensitivity, ACTH was naturally tried on other diseases of little known etiology. On many conditions, such as acute iridis, ACTH has produced almost spontaneous remission of symptoms. In others, the therapeutic results are still open to question, while in still other disease entities the symptoms were aggrevated. The era of indiscriminate use is drawing to a close and the greatest promise appears to lie in the fields of allergic and collagen diseases.

Just how is the response of the organism to trauma modified by adrenal stimulation? What are the different reaction patterns set up to the introduction of foreign substances and in particular foreign proteins, under adrenal-cortical stimulation? Is the general response similiar to that seen in physical trauma? In what manner, if any, are the antibody responses of the organism affected?

The response of a break in the skin, or open laceration, as compared to the normal healing reaction, has been shown to be markedly affected by adrenal-cortical stimulation, and to some extent by other hormonal secretions.

After complete adrenal extirpation, the healing process is only slightly delayed, granulation tissue possibly being somewhat inferior, while animals maintained on desoxycorticosterone wire shown to have a greatly enhanced healing response.[31,32] Taubenhaus[32] found the opposite to be true when animals were maintained on glucocorticoids. Whether stimulation is produced by ACTH or by 11 dehydro 17 hydroxycorticosterone, wound healing was shown to be markedly depressed. Ragan[23] first demonstrated that wounds in rabbit ears would show onto only very minimal evidence of healing when maintained on ACTH. All components of the healing process were delayed, andopen blood vessels could still be seen at the end of five days. Healing of fractures was also inhibited in a similar manner[4] There is a prolonged delay in resolution of the hematoma and after the fourth day differences become progressively more marked. Therefore, this interruption in healing is not limited to eqithelial tissues. Haber[28] has confirmed these early reports and in addition, found that cortisone is unable to produce lysis of granulation tissue already layed down in a wound. Just what effect these findings would mean to collagenous disease syndromes is unknown, but it would seem tc vitiate its usefulness in such diseases where pathologic tissue changes have already taken place.

Taubenhaus[32] found that sex hormones also caused a decrease in the healing response, similiar to that produced by ACTH, but not nearly as marked. The explanation for this is unknown, unless through their chemical structure they act similarly to cortisone. Thyroidectomy also is found to decrease the healing response. The growth hormone of the anterior pituitary was shown to increase wound healing, but since its effect was abolished by adrenalectomy, its stimulation more probably was through the adrenal cortex, causing liberation of desoxycorticosterone.

Just where, and in what manner, the healing response is interrupted is not known, although it has been shown that skin mitoses are inhibited by ACTH therapy.[12] This decrease in mitotic activity may be another factor in the decrease in lymphocytes shown in the peripheral blood. Since ACTH is an antagonist to hyaluronidase, wounds in ACTH treated animals were irrigated with hyaluronidase and still showed only superficial evidences of epithelialization and no real healing response.[3]

In general, it can be said from these findings that the normal healing response is only slightly diminished after adrenalectomy and this response is further deterred by sex hormones and almost completely stopped by ACTH and cortisone. However wounds treated by minerocorticoids (desoxycorticosterone) showed a marked increase in normal healing. Thyroid is probably a supporting factor because it increases metabolism of tissue in general.

Since reactivity of tissues to mechanical trauma is very noticeably diminished when stimulated by the glucocorticoids, as observed by Selve, the question arises as to what response, if any, might one suspect if the insulting agent were some foreign substance.

Relatively little work has been done until recently concerning the reticulo endothelial system in relation the pituitary adrenal system. Parodi (cited by Gordon) demonstrated a decrease in phagocytic activity in vitro after hypophysectomy which was restored by alkaline pituitary extract. Blanchard (reported by Gordon) found that adrenal cortical extract enhanced the opsonic powers of the blood. Experiments conducted on adrenalectomized and hypophysectomized animals have shown marked changes in the histiocytes and macrophages. In general, cells tend to undergo degenerative changes. The total number is decreased; the nuclei become pyknotic, the chromatin becomes dense, and the cytoplasm becomes vacuolated. These changes are most noticeable in the Kupffner cells of the liver, and to a lesser extent in the spleen, lymph nodes and bone marrow. There was also shown to be a decrease in the uptake of injected thorium. These changes can be almost completely reversed by giving ACTH or adrenal cortical extract, but not by desoxycorticosterone.[13] Haber[28] has shown, by injection india ink intra-peritoneally in mice, that there is no response or uptake in the mediastinal lymph nodes in those receiving ACTH as compared to untreated animals. It is difficult to correlate these two experiments since in one instance phagocytic

activity of the reticuloendothelial system was restored to normal by ACTH, and in the other, the normal response of an animal was lowered by excessive doses of ACTH. Green[12] believes that rapid spread of infection in these cases threated by ACTH is due to a blocking of the normal response of the reticulo endothelial system by blocking nucleo protein synthesis.

There has been a considerable amount of work done on the relation of the adrenal cortex to circulation antibody levels in the peripheral blood, and almost as much difference of opinion. Earlier work has been summed up by Herman.[16] Hektoen and Curtis 1915, found no change in antibody titer after adrenalectomy. Gates, 1918, found antibody formation unaffected by partial adrenalectomy. Jaffe and Marine, 1923-1924, found higher titers for the first three weeks but no appreciable change after six weeks. Mormonston-Gottesman and Perla in 1928 notes decreased rates of antibody formation after adrenalectomy, being most marked the first postoperative week. Fox and Whitehead, 1936, were the first to use adrenal cortical extract; they found an increased rate of antibody formation, but control animal eventually reached the same titer levels.

Eisen[9] in 1947 ran precipitin tests against type I pneumococcus. He reported only a very moderate (30%) increase incirculating antibodies. Since the adrenalectomized animals in this experiment were maintained on dexoxycorticosterone, and sodium chloride as well as ACTH, it is quite possible that they recieved more minerocorticoid than glucocorticoid stimulation, using the

theory of Selye. There also was no typical thymic atrophy as is normally the case when adrenal cortical extract is administered. Herbert[16] presents more conclusive proof; he was unable to show any rise in typhoid and staphalococcus antibody titers, nor any change in serum protein when as much as fifty mg. of ACTH was injected every hour to normal human beings. Nor could he find any difference when different levels of antibody titer were used. In these experiments the typical lymphoid dissolution was present. Bjorneboe and Stoerk (reported by Fischel)[10] found, not only no rise in titer, but an actual inhibition of antibody titer. The mortality rate in mice has not been changed by high maintenance levels of ACTH,[33] when injected with virulent pneumococci, even though the typical lymphoid atrophy was present; however, no actual antibody determinations were made. Experiments run on normal individuals show no changes in the electrophoretic pattern of the serum protein when receiving ACTH.[21] These diversified experiments would suggest that there exists no relationship between adrenal cortical activity and circulating antibody levels.

Almost the exact opposite in findings have been reported by White, Dougherty, and Chase, In 1944, White[34] demonstrated a fall in the circulating lymphocytes after the injection of adrenal cortical extract. It was suggested at this time that the dissolution of the lymphoctyes should cause a rise in the total serum protein. Since immune bodies have been found in the lymphocytes of rabbits,[14] experiments were conducted in which it was shown that there was an increase in the serum protein and in antibody titer,[5] at least in

the rabbit. The most marked rise occurred about 6 hours after injection, corresponding to the period of maximum lymphoid dissolution. This suggested that the rise in protein and antibody circulation was due to liberation from the dissolution of the lymphocytes in the circulating blood. Rabbits were injected with sheep red cells would, at the end of three months, show no demonstrable titer in the peripheral blood, but treated with ACTH, there would be a definite and marked rise in titer. The rise in titer was much more marked than if there had just been an injection of sheep cells.[6] These results are diametrically opposed to those of Fischel and Herbert and it is difficult to correlate them. This response was not shown by desoxycorticosterone, but this anamnestic response was still intact in adrenalectomized animals if adrenal cortical extract, 11 dehydro 17 hydroxycorticosterone, were substituted for ACTH. This work was further expanded and it was shown that the hemolysin titer to sheep red cells would rise faster and to higher levels when given concurrently with adrenal cortical extract. Also, there would be no fall in titer levels after the series of injections of sheep red cells had been terminated, so long as adrenal cortical extract continued to be administered.[7] Chase, in 1946, further expanded this work and got essentially the same results with mice, rats and rabbits, using staphalococcus toxin, egg albumin and horse sera as well as sheep red cells. He found very low antibody titer was formed if sex hormones were substituted for adrenal cortical ex-

tract in these experiments. Since a lymphopenia develops in the anamnestic response, they were also able to show antibody titer increases by using a wide variety of stimuli adaptable of producing such response. In summary, adrenal stimulation causes destruction of lymphocytes, liberating antibodies. The titer levels showed a greater response and reached higher levels when under adrenal cortical stimulation than if just the antigen was used.

The question arises as to what should be expected of other responses of the animal to the injection of foreign protein. It has long been known that adrenalectomy increases an animal's sensitivity to anaphalactic shock. Also, the anaphylactoid state is accelerated by desoxycorticosterone.[2] Anaphylaxis is closely related to allergic and antigen antibody reactions.

In general, allergy is localized while anaphylaxis is a generalized response. The same basic things take place in both, contraction of smooth muscle, dilatation of the capillaries, increased permeability of the capillaries, and increased glandular secretion. The exact role played by histamine is not known, though it can cause all of the foregoing conditions.

It has been shown that repeated injections of "cortin" raise an adrenalectomized animal's resistance to anaphylactic shock five fold,[22] but in these experiments resistance was not raised up to the original levels prior to adrenalectomy. Wolfram[36] found that mice could be protected from anaphylactic shock due to egg albumin by first giving cortin two to six hours prior to the sensitizing dose.

Guinea pigs sensitized to horse sera show the greatest percentage of survival if ACTH was administered two to five hours prior to the shock dose.[19] Dragstedt[8] showed that adrenal cortical extract does not prevent anaphylaxis from occurring in dogs but does modify the response in such a manner that a large number will survive an otherwise fatal dose. There was no change in the blood histamine levels, however, indicating that ACTH is not a pharmocological antagonist to histamine, nor does it block its formation. However, there is a marked increase in the histamine levels in adrenalectomized animals.[25]

Anaphylactoid hypersensitivity in rabbits can produce cardiac lesions and lessions similar to periarteritis, but these may be prevented if animals are placed on ACTH;[1] even though the lesions are prevented, they still show the same reactions to localized skin tests. With egg white as the sensitizing agent, shock was worsened by desoxycorticesterone and lessened by ACTH or cortisone.[27] Selye was also able to show the same amelioration of symptoms by any of the alarm producing stimuli. Here again, symptoms were worsened with DCA, and would go on to show arthritic and rheumatic changes. Anaphylactic shock was most marked if the animals were previously adrenalectomized, suggesting that the animals became sensitized to desoxycorticesterone or that there was an unbalance set up between the endogenous sources of gluco and minerocorticoids. Employing the use of Kabats quantitative technique[10] for inducing anaphulactoid reactions, in which the initial dose is injected locally and the anaphylactoid dose is given intravenously, shows no change from those which did not re-

ceive therapy. This experiment is really little different from a simple skin test, except that the response is generalized rather than localized. ACTH appears to be quite different in its action than the antihistaminics. ACTH has no effect on allergic wheals whether the hormone be given locally at the time of the pollen injection, before, at the site of the injection, or systemically before the pollen is injected. The same results were shown when plasma from a rag weed sensitive patient was injected intradermally into a non rag weed sensitive patient. The only difference shown after ACTH therapy, was a decrease in eosinophils at the skin test site, which corresponded to the circulating eosinophil levels in the blood.[37] These local reactions were all inhibited when antihistaminics were used.

Rose[25] 1950 reports that anaphylaxis is due mainly to histamine and since adrenalectomy causes a rise in the histamine and histamine metabolism is interfered with and collects in the tissues. He suggests that this may be due to the animals inability to inactivate histamine by histaminase. During pregnancy there is a marked increase in the histaminase in the urine and it is postulated that adrenal activity restores the normal histamine histaminase activity. There has also been reported marked decreases in the blood histamine levels when cases of Loefflers syndrome and Tropical eosinophilia[18] are treated with ACTH.

It has been pretty generally agreed that the anaphylactoid state and allergic state are very greatly reduced if treated with ACTH, but no conclusions appear to be in sight as to why ACTH in-

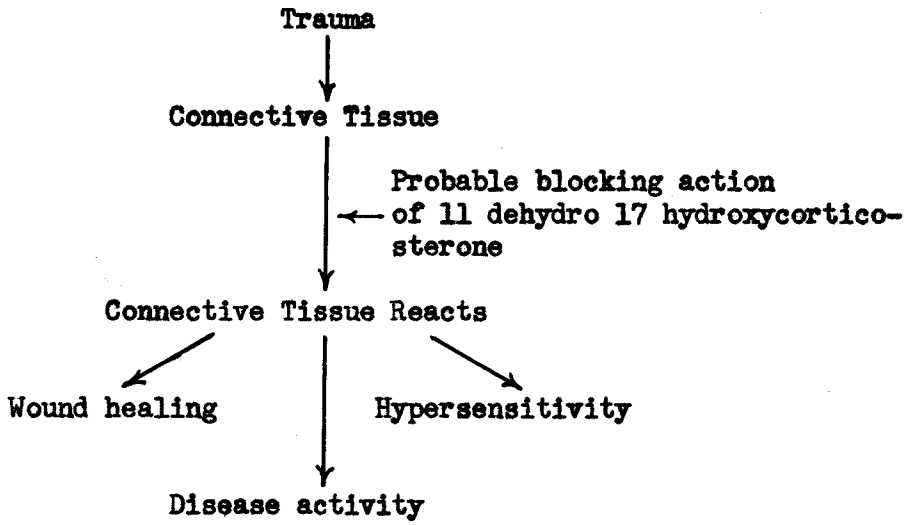
hibits the generalized manifestations of anaphylaxis and allergy but has no apparent effect on the localized signs. Kanee[20] feels that allergy is on cellular basis and the reaction of antigen and substrate liberate an H substance which cause the generalized manifestation of allergy. Just how histamine is tied in is not known at this time.

Conclusions

In general, it can be said that adrenal cortical activity decreases the response shown by the cells and tissues to external influences. This was definitely proven to be the case with physical trama, also with anaphylactoid and allergic reactions. Results are still equivocal concerning antigen antibody reactions and reticulo endothelial responses of the organism to stress. If the same generalizations can be applied, it would seem logical that there should also be a lack of response on the part of the reticulo endothelial system. More experimentation needs to be carried out to clarify the varying results thus far reported.

The adrenal cortex appears to secrete several different hormones, one series of which is antagonistic to another series, namely the glucocorticoids and minerocorticoids. Selye suggests that lipolized anterior pituitary extract (LAP) has similar action to desoxycorticosterone and that ATCH acts similarly to cortisone. Whether these hormones are not in proper balance in disease processes which respond to treatment with ACTH or cortisone, or whether there is a hypersensitivity on the part of the substrate for DCA is not known. The satisfactory therapeutic results obtained seem to be a function of the glucosteroids.

The effect of ACTH on collagen and mesenchymal tissues is not a well understood function of the adrenal gland. Just how products of the adrenals block the normal chain of events is not known, but at present it can be diagramed as follows.[24]



Adrenal cortical activity seems not to act against the etiologic agent of the disease process, but against the tissue reaction which accompanies the disease. It apparently provides a suitable buffer for the insulting agent and the adrenal products exert their effect upon the pathologic physiology rather than upon the etiology of the disease process.

Bibliography

1. BERTHRONG, M. Rich, A. Griffith, P. A study of the Effect of Adrenocorticotropic Hornone (ACTH) Upon Experimental Cardio Vascular Lesion Produced by Anaphalactoid Hypersensitivity. Bulletin of the Johns Hopkins Hospital V. 86: p 134 1909

2. BHEMENTHAL, J. S. Pituitary Adrenocorticotropic Hormone in Asthma. Minnesota Medicine V. 33; p 797 1950

3. CREDITOR, M., Bevan, M. Mundy, W., Ragan, C., Effect of ACTH on Wound Healing in Humans. Proceedings of the Society of Experimental Biology and Medicine. V. 74 p 245 1950

4. BLUNT, J., Platz, C., Lattes, F., Howes, E., Meyer, K., Ragan, C. Proceedings of the Society of Experimental Biology and Medicine. Effect of Cortisone on Experimental fractures in the Rabbit. V. 73; p. 678 1950

5. DOUGHERTY, T., Chase, J., White, A. Pituitary Adrenal Cortical Control of Antibody Relase from Lymphocytes; An Explanation of the Anamnestic Respnse. Proceedings of the Society of Experimental Biology and Medicine. V. 58 p 135 1945

6. DOUGHERTY, T., White, A. Relationship of the Effects of Adrenal Cortical Secretion on Lymphoid Tissue and on Antibody Titer. Proceedings of the Society of Experimental Biology and Medicine. V. 65 p 301 1947

7. DOUGHERTY, T., White, A., Chase, J. The Relationship of the Effects of Adrenal Cortical Secretion on Lymphoid Tissue and Antibody Titer. Proceedings of the Society of Experimental Biology and Medicine. V. 56 p. 28 1944

8. DRAGSTEDT, C., Mills, M., Mead, F. Adrenal Cortical Extract in Canine Anaphylactoid Shock. Journal of Pharmocology and Experimental Therapeutics. V. 59 p. 359 1939

9. EISEN, H., Meyer, M., Moore, D., Terr, R., Stoerk, H. Failure of Adrenal Cortical Activity to Influence Circulating antibodies and Gamma Globulin. Proceedings of the Society of Experimental Biology and Medicine. V. 61 p. 301 1947

10. FISCHEL, E. The Relationship of Adrenal Cortical Activity to Immune Responses. Bulletin of the New York Academy of Medicine. V. 17 p. 255 1950

11. FORTIER, C., Skelton, F. A Comparative Study of Some of the Chemical and Morphological Changes Elicited in the Adrenals by Stress and Purified ACTH. Endocrinology V. 27 p. 361 1940

12. GREEN, H. Suggested Mode of Action of Corticotropin in Rheumatoid Arthritis and the Allergic State. British Medical Journal. p. 1165 May 20, 1950

13. GORDON, A., Katsh, C., The Regulation of the Adrenal Cortex to the Structure and Phagocytic Activity of the Macrophagic System. Annals of the New York Academy of Sciences V. 52 p. 1 1949

14. HARRIS, T., Grimm, E., Mertens E., Eirich, W. The Role of the Lymphocyte in Antibody formation. Journal of Experimental Medicine. V. 81 p. 73 1947

15. HENCH, P., Kendall, E., Schocumb, C., Polley, H. Effect of Hormone of the Adrenal Cortex (17 hydroxy 11 dehydro cortico sterone), Compound E, and Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis. Proceedings of the Society Mayo Clinic V. 24 p. 181 1949

16. HERBERT, P., DeVries, J., Administration of Adrenocosticotropic Hormone to Normal Human Subjects and the Effect of the Leukocytes in the Blood and on Circulating Antibody levels. Endocrinology V. 44 p. 259 1949

17. HERBERT, P., DeVries, J., Rose, B., Studies of ACTH in a Case of Loefflers Syndrome and a Case of Tropical Eosinophilia Journal of Allergy V. 21 p. 12 1949

18. HILLS, G., Forsham. P., Finch, C. Changes in the Circulating Leukocyes Induced by Administration of ACTh in Man. Blood V. 3 p. 755 1948

19. JRSKOV, A., Little Experiment with ACTH in Anaphylactoid Shock Acta Pathologica and Microbiologica - Scandanavica Vol. 26 p. 6 1949

20. KANEE, B., Grant, J., Mallek, J. ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma. Canadian Medical Association Journal V. 62 p. 428 1950

21. MASON, Results of the Administration of ACTH to Norman Humans Journal of Biologic Chemistry V. 169 p. 223 1947

22. MORMORSTON-GOTTESMAN, J.,Perla, D., Effects of Injections of Cortin on Resistance of Suprarenalectomized Rats to Large Doses of Histamine. Proceedings of the Society of Experimental Biology and Medicine. V. 28 p. 1022 1931

23. RAGAN, C., Howes, E., Poltz, C., Meyer, K., Blunt, J. Effect of Cortisone on the Production of Granulation Tissue in the Rabbit. Proceedings of the Society of Experimental Biology and Medicine. V. 72 p. 718 1949

24. RAGAN, C., Howes, E., Poltz, C., Meyer, K., Blunt, J. The Effect of ACTH and Cortisone on Connective Tissue. Bulletin of the New York Academy of Medicine Apr. 1950 Vol. 52 Art. 4 1950

25. ROSE, B., Pare, J., Pump, K., Stanfort, R., Preliminary Report on Adrenocorticotropic Hormone (ACTH) in Asthma Canadian Medical Addociation Journal V. 62 p. 6 1950

26. SELYE, H. Theory of Adaptation and Diseases of Adaptation. Journal of Clinical Endocrinology V. 6 p. 117 1946

27. SELYE, H. Effect of ACTH and Cortisone Upon Anaphylactoid Reactions. Canadian Medical Association Journal V. 61 p. 553 1949

28. SPAIN, D., Mortomist, N., Haber, A., Biologic Studies of Cortisone in Mice. Science V. 112 p. 335 1950

29. SPIES, T., Stone, R. Pituitary Adrenocorticotropic Hormone (ACTH) as a Tool of Clinical And Laboratory Research. V. 258 p. 12 1949

30. TABLOT, J., Lever, W., Consolazio, W. Metabolic Studies of Patients with Pimphigus. Journal of Investigative Dermatology V. 3 p. 131 1940

31. TAUBLNHAUS, M., Influence of Steroid Hormones on Granulation Tissue. Endocrinology V. 44 p. 359 1949

32. TAUBENHAUS, M., Amronina G., Effects of the Hupophysis, Thyroid, Sex Hormones and the Adrenal Cortex upon Granulation Tissue. Journal of Laboratory and Clinical Medicine V. 36 p. 7 1950

33. U. S. Naval Medical Research Institute, Bethesda Md. Failure of Adrenal Cortical Extract to Modify Immunity Acquired by Intact Mice through use of Pneumococcal Vaccine. 1949

34. WHITE, A., Dougherty, T. Influence of Pituitary Adrenocorticotropic Hormone on Lymphoid Tissue Structure in Relation to Serum Proteins. Proceedings of the Society of Experiamental Biology and Medicine. V. 56 p. 26 1944

35. WHITE, A., Dougherty T., Chase, J. The Enhancement of Circulatory Antibody Concentration by Adrenal Cortical Hormones. Journal of Immunology V. 52 p. 101 1946

36. WOLFMAN, J., Lwemer, R. Cortin Protection Against Anaphylactic Shock in Gunea Pigs. Journal of Experimental Medicine V. 61 p. 9 1935

37. ZELLER, M., Randolf, T., Collins, J. Adrenocorticotropic Hormone (ACTH), Gross and Histologic Effects on Skin Tests and Passive Transfer. Annals of Allergy Vol. 8 No. 2 91 163 1950