THE NUTRITIONAL ASPECTS OF CERTAIN ENDOCRINE DISTURBANCES*

GERSON R. BISKIND, M.D., AND MORTON S. BISKIND, M.D.

From the Departments of Pathology, Mount Zion Hospital and the University of California Medical School, San Francisco, California and the Endocrine Laboratory and Clinic, Beth Israel Hospital, New York, New York

Viewed in retrospect, numerous observations published during the past several decades have indicated a relationship between alterations of the nutritional state and endocrine disturbances, but these observations were either neglected, or misinterpreted, and did not attain the significance they deserved. With recent developments in the knowledge of nutrition and refinements in materials and technics, it has become possible to correlate a group of endocrine syndromes with impairment of hepatic function on a nutritional basis.

Soon after the isolation of the first crystalline estrogen, it became apparent that this and related steroids are rapidly inactivated in the body.[15, 28, 41, 49, 68, 84, 85] The literature on the earlier studies has been reviewed elsewhere.[23]

In an effort to elucidate the metabolism of the sex-endocrine steroids, the senior author, some eight years ago, devised an efficient technic for studying the problem in the intact animal. When a pellet of estrone, estradiol or estradiol benzoate was placed in the spleen of a castrate rat, so that the absorbed steroid first had to pass through the liver before reaching the systemic circulation, no estrogenic effect was demonstrable; nor was there an androgenic effect when pellets of testosterone, testosterone propionate or methyl testosterone were placed in the spleen. The livers of both male and female rats inactivated both estrogens and androgens. Transplantation of the spleen containing the pellet of steroid, and ligation of the pedicle after establishment of a collateral circulation, produced the specific estrogenic or androgenic effect according to the nature of the implanted pellet.[9, 10, 11, 12, 13] There have been many other reports since these on the ability of the liver to destroy estrogens and androgens and there is now little doubt that inactivation of the sex hormones takes place in the liver.[46, 65, 66, 67, 68, 81]

During the period that our observations were being made, there were many reports concerning the production of hepatic lesions by nutritional deficiency.[1, 42, 43, 44, 45, 55, 56, 60, 61, 62, 64] The method of splenic implantation of pellets of steroids immediately lent itself as a method of observing the effects of certain aspects of nutrition in relation to hepatic function. We found that castrate female rats with pellets of estrone in their spleens remained anestrous when on a normal diet, but went into continuous estrus when the diet was depleted in the B complex vitamins. The addition of brewers yeast, or a mixture of crystalline thiamine, riboflavin, pyridoxine, and calcium pantothenate to the diet restored

* Aided by grants from Lederle Laboratories, Inc. and The Upjohn Company. Presented at the Twenty-Fourth Annual Meeting of the American Society of Clinical Pathologists, in San Francisco, June 29, 1946. Received for publication, September 7, 1946.

the anestrous state. Subsequent depletion of the vitamins again led to continuous estrus. The inactivating mechanism in the liver bears no necessary relation to detectable morphologic changes, since impairment of the mechanism took place in livers that appeared normal histologically, while inactivation can occur in livers that show necrosis and fat infiltration.[17, 18, 20, 21, 23, 27]

Subsequent investigation of estrogenic inactivation of the liver indicates that in acute experiments, *in the rat*, thiamine and riboflavin alone, among the B vitamins, are adequate to permit hepatic destruction of estrogen.[65, 67, 69] The presence of methionine appears essential to this function.[46, 81]

Our studies were continued by analyzing the effect of these nutritional changes on the metabolism of androgen in the liver. The technics employed were similar. In contrast to the effect observed with the estrogens, there was no *significant* impairment of the ability of the liver to destroy androgen in deficiency of vitamin B complex.[23] This observation indicated an alteration of the estrogen-androgen equilibrium and suggested a series of clinical studies on the relation of nutritional deficiency to syndromes in which this balance is disturbed. This soon led us to the development of a rational method of therapy.[16, 19, 22, 24, 26]

The fundamental work of R. T. Frank and his collaborators[31, 32, 33, 34, 35] showed that certain forms of pathologic uterine bleeding, of premenstrual tension, and of chronic cystic mastitis were related to an excess of estrogen. Originally, these were thought to be caused by an excessive secretion of estrogen by the ovaries. However, in view of our observations that the liver loses its power to destroy estrogen in deficiency of vitamin B complex, the relation of these syndromes to nutritional deficiency was investigated.

Liver poisons and cirrhosis of the liver have long been known to produce menorrhagia and metrorrhagia.[51, 63] The work of György and Goldblatt,[43, 44, 45] and others has shown that cirrhosis of the liver can result from nutritional deficiency. The liver is protected against a variety of poisons by vitamin B complex.[1, 29, 30, 52, 53, 56, 60, 78, 82] Goldberger[40] reported that menorrhagia may occur in pellagra. In male patients with cirrhosis of the liver, urinary estrogen is increased and appears in the free form, while urinary androgen is reduced and is present only in combined form;[38, 39] these patients had gynecomastia, testicular atrophy, or both. Changes related to excess estrogen occur in the prostate glands and in the testes of patients with cirrhosis of the liver.[55, 83] A study of necropsy data on female patients who died of cirrhosis of the liver[14] invariably revealed lesions in the pelvic organs identical with those induced by estrogenic stimulation. Even aged female patients dying of hepatic cirrhosis have a hyperplastic endometrium in the proliferative phase (G. R. Biskind, unpublished). The cutaneous vascular spiders and palmar erythema, formerly associated mainly with cirrhosis of the liver, have been shown by Bean[4, 5, 6, 7] to be related to nutritional deficiency, and to the presence of estrogen in increased amounts. Administration of estrogen to patients with these cutaneous phenomena produced new lesions and exacerbation of those already present; regression followed withdrawal of estrogen. Those observations are correlated with those of Reynolds and Foster[59] who showed that estrogen causes dilatation

of the minute vessels in the ears of castrated rabbits; and Bean has shown that the cutaneous vascular spiders are histologically similar to the spiral arteries of the endometrium observed by Bartelmez[3] and by Jones and Brewer[50]. Palmar erythema has been noted by Perera[58] in nutritional deficiency and the regression of this lesion has been described in two cases of cirrhosis under dietary therapy. There have been many observations on the relation of estrogen to the menstrual cycle and to liver function, and these indicate that with increase in amount of body estrogen, either cyclically during the intermenstruum or in the latter part of pregnancy, there may be a concommitant drop in liver function.[47, 48, 79] Delayed postpartum involution of the uterus and its complication of subsequent menometrorrhagia, cystic mastitis and premenstrual tension occurs as a result of impairment of hepatic function with the associated increase in body estrogen.[14]

To summarize the experimental evidence: it is obvious from experimental observations *in vitro* and *in vivo* that the liver is the site of metabolic conversion of estrogens and androgens from physiologically active materials to inactive substances. The inactivation of estrogens in the liver is controlled by factors which influence the function of the liver, such as nutrition, poisons, and cirrhosis. Since metabolism of the androgens is not significantly effected by these factors, it becomes evident that serious alterations of the estrogen-androgen equilibrium in the body can occur on the basis of disturbances that impair hepatic function. With impairment of the estrogen-inactivating mechanism of the liver, there is a retention of body estrogen. The clinical evidences of excess estrogen in the female are menometrorrhagia, premenstrual tension, cyclic, painful enlargement of the breasts, chronic cystic mastitis, and if the condition is protracted, uterine myomas and other benign overgrowths, or malignant neoplasms of such tissues as uterus and breast, which are responsive to estrogen. The changes in the male are not quite so readily evident, but are equally frequent; these are testicular softening and atrophy, diminished libido and impotence, and infertility. Gynecomastia is also occasionally seen as a consequence of excess estrogen resulting from nutritional impairment of hepatic function. This lesion has recently been reported to have been quite common among our troops in the Pacific, who had been captured by the enemy and maintained for long periods on severely restricted diets. On the basis of our observations already described, the lesion was correctly related to the nutritional defect and it responded to dietary therapy. Thus, the basic etiologic factors in certain pathologic entities become clarified: the constant stimulus of a high estrogen level in the body produces an endometrium that remains in a proliferative state throughout the cycle, then slowly progresses into a permanent hyperplastic state with irregular bleeding. The same stimulus applied over a period of years to the myometrium can induce localized or irregular hypertrophies and hyperplasias of the muscle with ultimate isolation of a nodule and the formation of a leiomyoma. It is well known that these tumors are related to the estrogen level of the body; regression after the menopause is almost invariable. In the same manner, it is possible to understand the development of chronic cystic mastitis; the continuous and additional cyclic stimulation of the breasts over a period of many years can ultimately

lead to localized hyperplasia of glands and ducts; this is associated with irregular scarring or increase of fibrous tissue. That these hyperplastic lesions in the endometrium, cervix and in the breast can ultimately become malignant is readily understandable, and the recent study by Ayre and Bauld[2] on the relation of thiamine deficiency, high estrogen, and uterine cancer is a logical step which followed our earlier observations.

On the basis of experimental evidence that nutritional factors can control the metabolism of estrogen in the liver, patients exhibiting signs and symptoms of excess estrogen were studied. In every instance, it was possible to find evidence of nutritional deficiency in these patients; glossitis, cheilosis, and other signs of deficiency were observed and photographic records in color were made routinely before and after treatment with nutritional factors. Large doses of synthetic B complex vitamins were administered, together with adequate amounts of a crude natural source of accessory vitamin B factors, preferably as whole desiccated liver or the fractions of liver containing the highest concentration of the nutritional factors. In our more recent studies in man, the total daily dosage by mouth was given in divided doses after meals and consisted of 38 to 45 mg. of thiamine, 20 to 35 mg. of riboflavin, 12 to 25 mg. calcium pantothenate, 3 to 8 mg. pyridoxine, 200 to 300 mg. niacinamide, 200 mg. choline, 90 to 150 mg. inositol, and 180 to 300 micrograms of folic acid derived, in part, from crystalline material and, in part, from natural sources. Desiccated whole liver derived from 45 to 75 gm. of fresh liver, or liver fractions derived from 60 to 100 gm. of liver, or combinations of the two were administered. In some cases, it was necessary to supplement this with frequent intensive parenteral administration of synthetic B vitamins, since preparations of liver extract for parenteral use are refined mainly for their antianemia potency and thus have lost much of their effectiveness for nutritional therapy.

The results of this therapeutic program can now be evaluated on the basis of the authors' observation of three groups of patients, totalling more than 700, in widely separated communities, for periods up to five years, and on an additional large group reported to us in personal communications from physicians employing this program. The functional condition of the patients who were studied varied from simple premenstrual tension with slight mehorrhagia and mastalgia, to severe irregular metrorrhagia caused by cystic hyperplasia of the endometrium which is often associated with leiomyomata, or severe cystic mastitis of the breast. The response to intensive, persistent and complete nutritional therapy was invariably excellent in all the syndromes related to excess estrogen. After the endocrine disturbance has been controlled and the nutritional lesions healed, it was nearly always possible to reduce the intake of B complex, although this usually had to be continued indefinitely thereafter in from five to ten times the maintenance amounts for normal persons.[54] It is suggested that once tissues are depleted of these factors, changes may occur which require a greater amount of the vitamin than that needed for normal maintenance. Bessey and Lowry[8] found that the level of riboflavin in the rat cornea reflects the riboflavin intake, but that once the animal has been depleted of riboflavin, administration of ribo-

flavin fails to increase the content of the cornea to the original level. This appears to apply to the human being also, for higher levels must be maintained in depleted than in nondepleted individuals. It cannot be too strongly emphasized that adequate amounts of a satisfactory natural source of the nutritional factors must be included in the therapeutic regime. Failures will occur if only synthetic vitamin preparations are used, or if the amount of naturally-occurring material is insignificant, as in several commercial preparations which contain only a few grains of brewers yeast. In the management of premenstrual tension and mastalgia, if therapy is begun at the time of menstruation, definite changes will usually be noted at the next menstrual period and almost complete alleviation of symptoms will frequently be evident at the second period. With grossly irregular metrorrhagia, especially in individuals in whom the condition has existed for years, several months may be required to bring about regular cycles in which there is evidence of a secretory phase indicating ovulation. So-called "lumpy breasts" require a similar period of intensive treatment with equally satisfactory results; in a few instances, there has been a rapid retrogression of most of the irregular indurated masses, but one or two nodules have persisted. These were removed surgically and were found to be made up of scar tissue, nests of glands, dilated ducts, and small cysts.

On the basis of the experimental observations described, which in their broadest sense lead to the conclusion that there may be an impairment of hepatic function in certain nutritional deficiencies, investigation of other conditions related to impaired liver function was also undertaken. Experiments by Soskin *et al.*[70, 71, 72, 73, 74, 75, 76] have shown that in the maintenance of normal carbohydrate metabolism, the liver plays a basic rôle, and that the liver is the site of the refractory state in insulin resistance. In pancreatectomized dogs, the diabetic state was exacerbated and the insulin requirements increased when the basic diet was devoid of B vitamins; the addition of yeast or of synthetic B vitamins reduced the insulin requirement to its former level.[37] Biskind and Schreier [26] indicate that the liver may be so altered by nutritional deficiency that it can no longer respond to endogenous insulin, thus inducing a failure in normal carbohydrate metabolism. The occurrence of lesions of the tongue in diabetes now known to be characteristic of pellagra was mentioned years ago by Stockton[77] and changes in the central nervous system in these cases, now known to be characteristic of thiamine and niacinamide deficiency, were mentioned by Futcher.[36] Thiamine, riboflavin, niacinamide, pantothenic acid, cholein, ascorbic acid, and Vitamins A and D are all known to be involved in carbohydrate metabolism. The application of all these facts by M. S. Biskind and Schreier[26] led to the treatment of diabetes on a nutritional basis. They observed an invariable assotion of avitaminotic lesions with the diabetic state. Partial or complete restoration of carbohydrate balance occurred in 94 patients receiving intensive and persistent nutritional therapy and the associated avitaminotic lesions cleared up at the same time together with alleviation of associated syndromes related to excess estrogen. In 25 patients, striking reductions in blood sugar level occurred on nutritional therapy alone; the insulin requirement was reduced in 14 persons,

eliminated in 16 instances, and in 37 patients in whom it was left unchanged, the improvement in general health and well-being was striking.

Another point that requires discussion is the question of widespread low grade vitamin deficiency in the population as a whole. The tendency towards a highly purified diet, with a limitation of meat and whole grains and without vitamin supplements, may account for the presence of a much greater degree of nutritional deficiency in the population than is generally considered possible. The fact that in the average young female, the presence of various degrees of premenstrual tension, abdominal puffiness and premenstrual breast changes are considered normal concomitants of menstruation, is an indication that widespread deficiency is prevalent. All these signs and symptoms respond quickly to adequate nutritional supplements.

SUMMARY AND CONCLUSIONS

It has been demonstrated in experimental animals that the liver is the site of inactivation of estrogens and androgens and there is abundant evidence that these steroids are similarly metabolized in the human liver. The ability of the liver to metabolize estrogen is controlled by certain factors, among which is the intake of vitamin B complex. Inactivation of androgen in the liver proceeds without significant impairment even during deficiency of vitamin B complex. Thus, it appears that the estrogen-androgen equilibrium in the body is maintained by a normally functioning liver, and that the equilibrium can be altered by nutritional deficiencies which impair the ability of the liver to destroy estrogen. In females, the estrogen thus retained produces premenstrual tension, retention of body water, mastalgia, menometrorrhagia, chronic cystic mastitis and uterine myomas; following pregnancy, there is impaired involution of the uterus. In males, this syndrome leads to testicular atrophy, diminution in libido and potency, infertility, and gynecomastia. All these functional conditions respond readily to intensive and complete nutritional therapy; the organic changes likewise respond, although more slowly, and often less completely. Nutritional deficiency with the concomitant accumulation of excess estrogen and the consequent prolonged stimulation of tissues of the uterus and breast, may lead to the development of precancerous hyperplasias and ultimately, in certain cases, to definite malignancy. At the present time, we have demonstrated in a large series of patients that the clinical signs and symptoms related to excess estrogen can be controlled by a therapeutic program that employs an adequate dosage of all the known and unknown factors of the vitamin B complex. The significance of nutritional deficiency in diabetes and its consequent impairment of hepatic functions is discussed in relation to the aforementioned syndromes.

REFERENCES

1. Ando, T.: Experimentelle Leberkarzinomentstehung und Getreide. Gann, **32:** 252–257, 1938.
2. Ayer, J. E., and Bauld, W. A. G.: Thiamine deficiency and high estrogen findings in uterine cancer and in menorrhagia. Science, **103:** 441–445, 1946.
3. Bartelmez, G. W.: Glandular Physiology and Therapy. Chicago: A. M. A., 1942, Chapt. XIII.
4. Bean, W. B.: Note on development of cutaneous arterial "spiders" with palmar erythema in persons with liver disease and their development following administration of estrogens. Am. J. M. Sc., **204:** 251–253, 1942.

5. BEAN, W. B.: Acquired palmar erythema and cutaneous vascular "spiders". Am. Heart J., **25:** 463–477, 1943.
6. BEAN, W. B.: Cutaneous arterial spider; survey. Medicine, **24:** 243–331, 1945.
7. BEAN, W. B., SPIES, T. D., AND BLANKENHORN, M. A.: Secondary pellagra. Medicine, **23:** 1–77, 1944.
8. BESSEY, O. A., AND LOWRY, O. H.: Factors influencing riboflavin content of cornea. J. Biol. Chem., **155:** 635–643, 1944.
9. BISKIND, G. R.: Inactivation of methyl testosterone in castrate male rats. Proc. Soc. Exper. Biol. and Med., **43:** 259–261, 1940.
10. BISKIND, G. R.: Inactivation of estradiol and estradiol benzoate in castrate female rats. Endocrinology, **28:** 894–896, 1941.
11. BISKIND, G. R.: Inactivation of testosterone propionate by normal female rats. Proc. Soc. Exper. Biol. and Med., **46:** 452–453, 1941.
12. BISKIND, G. R.: Experimental demonstration of inactivation of certain sex steroid androgens and estrogens in vivo. Brunn, Med.-Surg. Tributes, 41–58, 1942.
13. BISKIND, G. R., AND MARK, J.: Inactivation of testosterone propionate and estrone in rats. Bull. Johns Hopkins Hosp., **65:** 212–217, 1939.
14. BISKIND, L. H., AND BISKIND, M. S.: Accelerated postpartum involution of uterus with vitamin B complex therapy. West. J. Surg., **52:** 266–270, 1944.
15. BISKIND, M. S.: Estrogenic substances: theelin. J. A. M. A., **100:** 1331–1338, 1933.
16. BISKIND, M. S.: Nutritional deficiency in etiology of menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension; treatment with vitamin B complex. J. Clin. Endocrinol., **3:** 227–234, 1943.
17. BISKIND, M. S.: Biochemical discussion group. New York: 1944.
18. BISKIND, M. S.: Combination of aqueous and lipoid extracts of liver in the therapy of nutritional deficiency. New York: 1944.
19. BISKIND, M. S.: Relation of nutritional deficiency to diminished libido and impotence in the male (to be published).
20. BISKIND, M. S., AND BISKIND, G. R.: Diminution in ability of liver to inactivate estrone in vitamin B complex deficiency. Science, **94:** 2446, 1941.
21. BISKIND, M. S., AND BISKIND, G. R.: Effect of vitamin B complex deficiency on inactivation of estrone in liver. Endocrinology, **31:** 109–114, 1942.
22. BISKIND, M. S., AND BISKIND, G. R.: Nutritional deficiency and maternal behavior. J. Clin. Endocrinol., **3:** 377, 1943.
23. BISKIND, M. S., AND BISKIND, G. R.: Inactivation of testosterone propionate in liver during vitamin B complex deficiency. Alteration of estrogen-androgen equilibrium. Endocrinology, **32:** 97–102, 1943.
24. BISKIND, M. S., BISKIND, G. R., AND BISKIND, L. H.: Nutritional deficiency in etiology of menorrhagia, metrorrhagia, cystic mastitis, and premenstrual tension; further observations on treatment with vitamin B complex. Surg. Gynec. and Obst., **78:** 49–57, 1944.
25. BISKIND, M. S., AND FALK, H. C.: Nutritional therapy of infertility in male, with special reference to vitamin B complex and vitamin E. J. Clin. Endocrinol., **3:** 148–153, 1943.
26. BISKIND, M. S., AND SCHREIER, H.: On significance of nutritional deficiency in diabetes. Exper. Med. and Surg., **3:** 299–316, 1945.
27. BISKIND, M. S., AND SHELESNYAK, M. C.: Effect of vitamin B complex deficiency on inactivation of ovarian estrogen in liver. Endocrinology, **30:** 819–820, 1942.
28. EVANS, H. M., AND BURR, G. O.: Increased efficacy of subcutaneous when compared with intraperitoneal administration of ovarian hormone. Am. J. Physiol., **77:** 518–521, 1926.
29. FORBES, J. C., AND MCCONNELL, J. S.: Crystallization of liver fraction protecting against necrosis from carbon tetrachloride or chloroform administration. Proc. Soc. Exper. Biol. and Med., **36:** 359–360, 1937.
30. FORBES, J. C., AND NEALE, R. C.: New preparation protecting against rat liver necrosis. Proc. Soc. Exper. Biol. and Med., **34:** 319–320, 1936.
31. FRANK, R. T.: Hormonal causes of premenstrual tension. Arch. Neurol. and Psychiat., **26:** 1053–1057, 1931.
32. FRANK, R. T.: Glandular Physiology and Therapy. Chicago: A. M. A., 1935, Chapt. XVI.
33. FRANK, R. T.: Sex hormones; their physiologic significance and use in practice. J. A. M. A., **114:** 1504–1512, 1940.
34. FRANK, R. T., GOLDBERGER, M. A., AND SPIELMAN, F.: Utilization and excretion of female sex hormone. Proc. Soc. Exper. Biol. and Med., **29:** 1229–1231, 1932.
35. FRANK, R. T., GOLDBERGER, M. A., AND SPIELMAN, F.: Present endocrine diagnosis and therapy; critical analysis based on hormone study in female. J. A. M. A., **103:** 393–402, 1932.
36. FUTCHER, T. B.: Osler's Modern Medicine. Vol. I. Philadelphia and New York: Lea and Febiger, 1907, 747–798.

37. GAEBLER, O. H., AND CISZEWSKI, W. E.: Effects of yeast or water soluble vitamins in experimental pancreatic diabetes. Endocrinology, **36:** 227–235, 1945.
38. GLASS, S. J., EDMONDSON, H. A., AND SOLL, S. N.: Sex hormone changes associated with liver disease. Endocrinology, **27:** 749–752, 1940.
39. GLASS, S. J., EDMONDSON, H. A., AND SOLL, S. N.: Excretion of estrogen after injection of estradiol and estrone into men with cirrhosis of liver. J. Clin. Endocrinol., **4:** 54–57, 1944.
40. GOLDBERGER, J.: Tice's Practice of Medicine. Vol. IX. (Revised by W. H. Sebrell). Hagerstown, Maryland: W. F. Prior Company, 1932, p. 205.
41. GOLDEN, JUNE B., AND SEVRINGHAUS, E. L.: Inactivation of estrogenic hormone of ovary by liver. Proc. Soc. Exper. Biol. and Med., **39:** 361–362, 1938.
42. GYÖRGY, PAUL: Experimental hepatic injury. Am. J. Clin. Path., **14:** 67–88, 1944.
43. GYÖRGY, P., AND GOLDBLATT, H.: Hepatic injury on nutritional basis in rats. J. Exper. Med., **70:** 185–192, 1939.
44. GYÖRGY, P., AND GOLDBLATT, H.: Choline as member of vitamin B_2 complex. J. Exper. Med., **72:** 1–10, 1940.
45. GYÖRGY, P., AND GOLDBLATT, H.: Observations on conditions of dietary hepatic injury (necrosis, cirrhosis) in rats. J. Exper. Med., **75:** 355–368, 1942.
46. GYÖRGY, P., AND GOLDBLATT, H.: Further observations on experimental dietary hepatic injury. Fed. Proc., **4:** 154–155, 1945.
47. HEILIG, R., AND KANTIENGAR, N. L.: Liver function in menstruation, Ann. Int. Med., **16:** 538–546, 1942.
48. HIRSHEIMER, A.: Synthesis and excretion of hippuric acid in pregnancy. Am. J. Obst. and Gynec., **29:** 395–405, 1935.
49. ISRAEL, S. L., MERANZE, D. R., AND JOHNSTON, C. G.: Inactivation of estrogen by liver; observations on fate of estrogen in heart-lung and heart-lung-liver perfusion systems. Am. J. M. Sc., **194:** 835–843, 1937.
50. JONES, H. O., AND BREWER, J. I.: Arterial phenomena associated with uterine bleeding in tubal pregnancy. Am. J. Obst. and Gynec., **38:** 839–861, 1939.
51. KELLY, H. O. J.: Osler's Modern Medicine. Vol. V. Philadelphia: Lea and Febiger, 1908, p. 775.
52. KENSLER, C. J., SUGIURA, K., AND OTHERS: Partial protection of rats by riboflavin with casein against liver cancer caused by dimethylaminoazobenzene. Science, **93:** 308–310, 1941.
53. KENSLER, C. J., SUGIURA, K., AND RHOADS, C. P.: Coenzyme I and riboflavin content of livers of rats fed butter yellow. Science, **91:** 623, 1939.
54. MARTIN, H., AND KOOP, C. E.: Precancerous mouth lesions of avitaminosis B; their etiology, response to therapy and relationship to intra-oral cancer. Am. J. Surg., **57:** 195–225, 1942.
55. MORRIONE, T. G.: Effect of estrogens on testis in hepatic insufficiency. Arch. Path., **37:** 39–48, 1944.
56. NAKAHARA, W., FUJIWARA, T., AND MORI, K.: Inhibiting effect of yeast feeding on experimental production of liver cancer. Gann, **33:** 57–65, 1939.
57. NAKAHARA, W., AND MORI, K.: Experimental production of liver cirrhosis by furfural feeding. Gann, **35:** 327, 1941.
58. PERERA, G. A.: Note on palmar erythema (so-called liver palms). J. A. M. A., **119:** 1417–1418, 1942.
59. REYNOLDS, S. R. M., AND FOSTER, F. I.: Peripheral vascular action of estrogen, observed in ear of rabbit. J. Pharmacol. and Exper. Therap., **68:** 173–184, 1940.
60. RHOADS, C. P.: Physiological aspects of vitamin deficiency. Proc. Inst. Med. Chicago, **13:** 198–205, 1940.
61. RHOADS, C. P., AND MILLER, D. K.: Hepatic dysfunction in dogs fed diets causative of black tongue. J. Exper. Med., **67:** 463–467, 1938.
62. RICH, A. R., AND HAMILTON, J. D.: Experimental production of cirrhosis of liver by means of deficient diet. Bull. Johns Hopkins Hosp., **66:** 185–198, 1940.
63. ROLLESTON, H. D.: Diseases of the Liver, Gallbladder, and Bile Ducts. London: Macmillan, 1912, p. 278.
64. SEBRELL, W. H., AND ONSTOTT, R. H.: Riboflavin deficiency in dogs. Pub. Health Rep., **53:** 83–94, 1938.
65. SEGALOFF, ALBERT, AND NELSON, W. O.: Absorption and metabolism of estrogens; estrogen assay by intrasplenic injection. Proc. Soc. Exper. Biol. and Med., **48:** 33–34, 1941.
66. SEGALOFF, ALBERT, AND SEGALOFF, ANN: Role of vitamines of B-complex in estrogen metabolism. Endocrinology, **34:** 346–350, 1944.
67. SHIPLEY, R. A., AND GYÖRGY, P.: Effect of dietary hepatic injury on inactivation of estrone. Proc. Soc. Exper. Biol. and Med., **57:** 52–55, 1944.
68. SILBERSTEIN, F., MOLNAR, K., AND ENGEL, P.: Über das Auftreten eines Brunststoffes im Blut und Geweben unter pathologischen Verhältnissen; über Zerstörung von Menformon im Blut und in Organen. Klin. Wchnschr., **12:** 1694–1695, 1933.

69. SINGHER, H. O., KENSLER, C. J., TAYLOR, H. C., RHOADS, C. P., AND UNNA, K.: Effect of vitamin deficiency on estradiol inactivation by liver. J. Biol. Chem., **154:** 79–86, 1944.
70. SOSKIN, SAMUEL: Blood sugar: its origin, regulation, and utilization. Physiol. Rev., **21:** 140–193, 1941.
71. SOSKIN, SAMUEL: Role of endocrines in regulation of blood sugar. J. Clin. Endocrinol., **4:** 75–88, 1944.
72. SOSKIN, S., ALLWEISS, M. D., AND COHN, D. J.: Influence of pancreas and liver upon dextrose tolerance curve. Am. J. Physiol., **109:** 155–165, 1934.
73. SOSKIN, S., ALLWEISS, M. D., AND MIRSKY, I. A.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function. Arch. Int. Med., **56:** 927–934, 1935.
74. SOSKIN, S., ESSEX, H. E., HERRICK, J. F., AND MANN, F. C.: Mechanism of regulation of blood sugar by liver. Am. J. Physiol., **124:** 558–567, 1938.
75. SOSKIN, S., AND LEVINE, R.: Experimental insulin-sensitive and insulin-insensitive diabetes. J. A. M. A., **110:** 768, 1938.
76. SOSKIN, S., AND MIRSKY, I. A.: Influence of progressive toxemic liver damage upon dextrose tolerance curve. Am. J. Physiol., **112:** 649–656, 1935.
77. STOCKTON, C. G.: Osler's Modern Medicine. Vol. V. Philadelphia and New York: Lea and Febiger, 1908, p. 55.
78. SUGIURA, K., AND RHOADS, C. P.: Experimental liver cancer in rats and its inhibition by rice-bran extract, yeast and yeast extract. Cancer Research, **1:** 3–16, 1941.
79. SULLIVAN, C. F., TEW, W. P., AND WATSON, E. M.: Bilirubin excretion test of liver function in pregnancy. J. Obst. and Gynec., Brit. Emp., **41:** 347–368, 1934.
80. SUTTON, D. C., AND ASHWORTH, J.: Interrelation between vitamin B complex and anterior lobe of pituitary gland. J. Lab. and Clin. Med., **25:** 1188–1192, 1940.
81. UNNA, K., SINGHER, H. O., KINSLER, C. J., TAYLOR, H. C., AND RHOADS, C. P.: Effect of dietary protein on liver riboflavin levels and on inactivation of estradiol by liver. Proc. Soc. Exper. Biol. and Med., **55:** 254–256, 1944.
82. VON GLAHN, W. C., AND FLINN, F. B.: Effect of yeast on incidence of cirrhosis produced by lead arsenate. Am. J. Path., **15:** 771–781, 1939.
83. WU, S. D.: Anatomic changes in prostate of patients with cirrhosis of liver. Arch. Path., **34:** 735–741, 1942.
84. ZONDEK, BERNHARD: Fate of follicular hormone in living body. Lancet, **2:** 356, 1934.
85. ZONDEK, BERNHARD: Über das Schicksal des Follikelhormons (Follikulin) im Organismus. Skandinav. Arch. f. Physiol., **70:** 133–167, 1934.