

VI. EFFECT OF OTHER HORMONES UPON RESISTANCE

← ACTH

Steroids ←

The influence of ACTH upon various actions of mineralocorticoids (*Selye C92,918/61, p. 18; G60,083/70, pp. 328–332*) and MAD (*Selye G60,083/70, pp. 328, 330*) has been discussed elsewhere. Let us add here that in rats ACTH (like adrenocortical extract) antagonizes many manifestations of overdosage with DOC, such as the: hypernatremia, EST-elevation, and insulin hypersensitivity, as well as the hyalinosis syndrome produced after uninephrectomy + NaCl. Conversely, the hyalinosis elicited by MAD is actually aggravated by ACTH. This singular “DOC-like” effect is presumably due to the inhibition by MAD of 11 β -hydroxylation in the adrenals; in the presence of this enzymic defect the corticotrophic action of ACTH shifts towards an excess secretion of DOC which has no 11 β -OH group.

Nonsteroidal Hormones and Hormone-Like Substances ←

ACTH shares with the glucocorticoids the property of increasing insulin resistance. This action is not unexpected in view of the antagonistic effect exerted by insulin and glucocorticoids upon the blood sugar.

In guinea pigs exposed to histamine spray, ACTH has little if any protective effect but the gastric ulcers produced in this species by conjoint treatment with histamine and antihistamines can be prevented by the concurrent administration of ACTH. In newborn rats, fatal histamine intoxication is not significantly influenced either by ACTH or by various glucocorticoids.

The production of renal infarcts by 5-HT in the rat, though diminished by hypophysectomy, is not significantly influenced by ACTH.

Steroids ←

Woodbury et al. B47,201/50: In rats, ACTH and adrenocortical extract antagonize the following actions of DOC: 1) hypernatremia; 2) EST threshold elevation; 3) insulin hypersensitivity; 4) hyalinosis (after sensitization by uninephrectomy plus NaCl).

Molteni et al. H4,919/68: In rats, the vascular lesions produced by MAD following uninephrectomy plus NaCl are aggravated by

ACTH, presumably, because MAD interferes with β -hydroxylation in the adrenals, so that under the influence of ACTH an excess of DOC is secreted.

Cortisol ← ACTH: Kuipers et al. C48,349/58*; Kumagai et al. C57,345/58; Berliner et al. G75,988/61*; Moor et al. G75,989/61*; Werk et al. F20,780/64*

Cortisone ← ACTH + Sex: Hagen et al. G77,512/60

Nonsteroidal Hormones and Hormone-Like Substances ←

Insulin ←. *Jensen & Grattan 77,887/40:* In mice, ACTH, glucocorticoids and cortical extracts increase insulin resistance, whereas other pituitary hormones and thyroxine have no such effect.

Thyroxine ← cf. Selye G60,083/70, pp. 328, 330, 347, 355.

Histamine and 5-HT ←. *Andreani B63,732/50:* In guinea pigs, conjoint treatment with large doses of histamine and antihistamines had previously been shown to result in gastric ulcer formation although the lethal effects of histamine are suppressed. These ulcers can be prevented by ACTH.

Friedlaender & Friedlaender B55,467/50: In guinea pigs, intoxication with histamine (aerosol) and anaphylactic shock (horse serum)

were not influenced by pretreatment with ACTH.

Buttle & Squires B59,985/51: In guinea pigs exposed to histamine spray, the time required to induce convulsions is prolonged by ACTH i.p. but only during approximately an hour after the injection.

Malkiel G71,451/51: In guinea pigs, ACTH and cortisone are without effect on the end results of histamine shock, or of passive or active anaphylaxis.

Jasmin & Bois C92,099/60: Hypophysectomy partially protects the rat against the production of renal infarcts by 5-HT. ACTH does not affect this change, cortisol aggravates it, whereas DOC and testosterone offer partial protection.

Schapiro F31,856/65: In newborn rats, fatal intoxication with histamine was not significantly influenced by ACTH, cortisol, cortisone or corticosterone.

Drugs ←

The effect of ACTH upon various intoxications has been the subject of many investigations; these could hardly be condensed more than has been done in the Abstract Section to which the reader is therefore referred. Here, we shall comment only on a few particularly interesting data and on certain observations which can be clarified by correlating them with facts not mentioned by the authors of the original articles cited.

Anaphylactoid edema is essentially a special type of serous inflammation, usually studied in rats because these are particularly sensitive to this change. The edema is more or less selectively localized to the acral regions (snout, paws, ears) and is ascribed to the sudden liberation of histamine and 5-HT from the mastocytes of the affected parts. It is provoked by so-called "anaphylactoidogenic agents," such as egg-white, dextran, polymyxin and other typical dischargers of histamine and 5-HT. Like most types of inflammation, this response can be prevented by ACTH and glucocorticoids but only if very large amounts are given. It is noteworthy however, that the specific toxicity of anaphylactoidogenic agents may be uninfluenced or actually aggravated by ACTH, even when the hormone suppresses inflammation itself.

Certain anticoagulants such as bishydroxycoumarin (Dicoumarol) and polyanethol sulfonate (Liquoid), at doses normally well tolerated by rabbits, cause death with widespread hemorrhages when given conjointly with ACTH. Curiously bishydroxycoumarin administered with glucocorticoids (cortisol, cortisone) does not elicit this syndrome.

In mice, ACTH shortens sleeping time after treatment with various barbiturates, including barbital, thiopental and pentobarbital. The induction time of barbital anesthesia was not changed but its depth was diminished in mice by cortisone, cortisol or ACTH. At the same time the barbital concentration of the brain was decreased by these hormones, which presumably protect against anesthesia by inhibiting

the barbital uptake of the brain. Compound "S" or DOC does not share these effects.

In the rat and in man, ACTH also shortens barbiturate sleeping time. Hexobarbital anesthesia is likewise diminished in rats by exposure to stress, presumably as a consequence of endogenous ACTH secretion.

It is highly probable that most of the barbiturates are detoxified by hepatic microsomal enzymes and some of the hormones which shorten barbital sleeping time may do so by inducing such enzymic activities. However, barbital is not significantly degraded within the body and hence, in this case the effect of ACTH is likely to be mediated through a different mechanism, perhaps a topical effect upon the cerebral barbital uptake.

In rats with tourniquet stress, the toxicity of hexobarbital, pentobarbital, meprobamate and zoxazolamine was significantly diminished, whereas that of barbital and phenobarbital remained unaffected. Pretreatment with ACTH or corticosterone simulated the effects of stress.

In rats, the organ changes produced by certain carcinogens are not regularly influenced by ACTH. However, hepatoma formation by N-OH-FAA is enhanced both by ACTH and by STH.

Prostatic carcinogenesis after topical 20-methylcholanthrene crystal implantation is inhibited by ACTH as well as by several thyroid and steroid hormones.

In mice, the amyloidosis produced by repeated parenteral administration of casein is aggravated by ACTH or glucocorticoids and it may be combined with waxy degeneration of the cardiac muscle.

The typical cholesterol atherosclerosis of the rabbit is diminished by ACTH as well as by several glucocorticoids. It is not clear as yet, however, whether this effect is due to increased cholesterol degradation by hepatic microsomal-enzyme systems or to some other, possibly local, effect of glucocorticoids upon the vessels.

In rats, fatal intoxication with certain ganglioplegics (TEA, hexamethonium, pentolinium) has been prevented by all glucocorticoids tested (triamicinolone, cortisol, prednisolone, etc.) but not by typical catatoxic steroids (ethylestrenol, CS-1, spironolactone, norboethrone, oxandrolone) or by progesterone, DOC and hydroxydione. Various stressors (bone fractures, fasting, spinal cord transection, formalin) gave excellent protection against TEA, whereas others (restraint, cold) did not. Since even large doses of ACTH failed to protect against TEA the prophylactic effect of stress cannot be ascribed exclusively to increased production of ACTH. The protective effect of glucocorticoids is not directed against ganglioplegics as such since these steroids offer no protection against trimethaphan, mecamylamine, trimethidinium or pempidine.

Although osteolathyrism produced in rats by lathyrogens (AAN, PNA, or the feeding of lathyrus seeds) is readily prevented by small doses of glucocorticoids, very large amounts of ACTH are required to obtain even partial protection. The dissecting aneurysms of the aorta characteristic of angiolathyrism are likewise readily suppressed by cortisone but not by ACTH.

The toxicity of morphine is diminished by ACTH in various species.

In guinea pigs, ACTH (like cortisone) ameliorates the manifestations of vitamin-C deficiency.

In rats, the generalized calcinosis produced by various vitamin-D and DHT preparations is aggravated by ACTH (as it is by glucocorticoids) but the development of rickets on vitamin-D deficient diets is not significantly affected by ACTH. These findings should be checked under varying experimental conditions of dosage and timing, since it is known that all potent catatoxic steroids prevent acute DHT intoxication in the rat, whereas only the anabolics appear to offer protection against chronic overdosage with the same compound. Indeed, catatoxic steroids with little or no anabolic potency (e.g., PCN, spironolactone) tend to aggravate DHT intoxication and to antagonize the beneficial effect of anabolic catatoxic steroids (e.g., ethyl-estrenol) in long lasting experiments.

Acetaldehyde ←

Lecog et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites, pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appeared to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Acrylonitrile ←

Szabó & Selye G79,010/71: In rats, pretreatment with ACTH (but not with STH) prevents the production of adrenal apoplexy by acrylonitrile. Hypophysectomy protects against adrenal apoplexy, but not against mortality under similar conditions.

Allylformiate ←

Küchmeister et al. B84,244/53: In rats, ACTH offers some protection against the hepatic damage produced by allylformiate.

Allylformiate ← ACTH: Küchmeister et al. B84,244/53*

Aminocaproic Acid ←

Pataki F75,591/67: In rabbits, combined treatment with polyanetholsulfonate (Liquoid) + EACA produces thrombohemorrhagic necrosis of the adrenal cortex. Simultaneous ACTH treatment significantly reduces the number of fibrin thrombi and the extent of adrenal necrosis but enhances the cortical hemorrhages.

Aminopterin ←

Traina B72,887/51: In mice, ACTH does not influence the toxic effects of aminopterin.

Aminopterin ← ACTH, Gp., Mouse: Traina B72,887/51*

Aminopyrine ← ACTH: Kato et al. F57,817/65

Anaphylactoid Edema ← cf. also Selye B40,000/50, p. 756; G46,715/68, pp. 177, 178, 183.

Higginbotham & Dougherty C44,529/57: In mice, ACTH increased the toxicity of polymyxin B; STH and TTH had no effect upon it.

Anticoagulants ←

van Cauwenberge & Jaques C58,521/58: A dose of phenindione or bishydroxycoumarin, well tolerated by otherwise untreated rabbits, causes death with widespread hemorrhages when given together with ACTH. The hemorrhagic tendency induced by bishydroxycoumarin was not accentuated by STH, cortisone or DOC.

van Cauwenberge & Jaques C72,748/59: The "hemorrhagic death syndrome" produced by dicoumarol treatment in rats simultaneously exposed to various stressors can be reproduced by the administration of ACTH, STH or DOC, instead of stressors. Dicoumarol + cortisol or cortisone did not reproduce this syndrome.

Pataki F75,591/67: In rabbits, combined treatment with polyanetholsulfonate (Liquoid) + EACA produces thrombohemorrhagic necrosis of the adrenal cortex. Simultaneous ACTH treatment significantly reduces the number of fibrin thrombi and the extent of adrenal necrosis but enhances the cortical hemorrhages.

Arsenic ←

Beck & Voloshin B58,271/50: In mice, resistance to arsenite and other arsenicals is increased by cortisone, adrenocortical extracts and ACTH.

Beck B64,609/51: "Prior administration of beef adrenal extract increased the resistance of mice, particularly male mice, to semi-lethal

doses of arsenite, oxphenarsine and clorarsen. Male mice were protected against arsenite by cortisone and ACTH, but not by desoxy-corticosterone."

Barbiturates ←

Hoyrup & Vinten-Johansen B84,197/52: In patients with acute phenobarbital or diphenylhydantoin poisoning, the use of ACTH is contraindicated as judged by impressions gained from a small series of observations.

Winter & Flataker B73,509/52: Cortisone or ACTH, unlike DOC, shortens barbiturate anesthesia. The markedly prolonged sleeping time of mice receiving both barbiturates and diphenhydramine is also decreased by cortisone but the effect of the steroid can be fully accounted for by its antagonism to the barbiturate.

de Boer & Mukomela C5,245/55: In rats, ACTH and cortisone shorten thiopental and pentobarbital anesthesia, especially in females whose sleeping time is normally longer than that of males.

Komiya C8,533/55: In mice, barbital sleeping time is decreased by cortisone, cortisol and ACTH but not affected by compound S (11-desoxocortisone) or DOC.

Komiya et al. C21,326/56: In mice, thiopental anesthesia is reduced in depth, but not in duration, by epinephrine. Barbital anesthesia was slightly reduced by norepinephrine but not by epinephrine. Unpublished experiments suggest that ACTH and glucocorticoids shorten the duration of barbital anesthesia in mice.

Komiya & Shibata C16,708/56: In mice, the induction time of barbital anesthesia was not changed by cortisone, cortisol, 11-desoxycortisone or DOC. The duration of anesthesia was shortened, the depth of anesthesia diminished, and the barbital concentration of the brain decreased by cortisone, cortisol or ACTH, but none of these parameters was affected by 11-desoxycortisone or DOC. Apparently, the active hormones protect against anesthesia by decreasing the barbital concentration of the brain.

Kubota & Bernstein C52,401/57: In man, ACTH ameliorates the symptoms of intoxication with various barbiturates.

Rupe et al. E26,910/63: The sedative effect of hexobarbital and pentobarbital but not of barbital was diminished by tourniquet stress, in the intact but not in the hypophysectomized

or adrenalectomized rat. In intact rats, ACTH or cortisone decreases hexobarbital sleeping time as does stress, whereas SKF 525-A completely blocks the protective action of stress. Presumably "the stress effect on the duration of drug action is mediated through increased drug metabolism."

Bousquet et al. E39,107/64: Morphine-pretreated rats sleep longer than controls after hexobarbital or meprobamate, but not after barbital. ACTH-pretreatment overcomes the morphine inhibition of drug metabolism (verified *in vitro*).

Bousquet et al. F35,073/65: In rats with stress produced by applying a tourniquet around one hind limb for 2.5 hrs, the toxicity of hexobarbital, pentobarbital, meprobamate and zoxazolamine was significantly diminished, whereas that of barbital and phenobarbital remained unaffected. Pretreatment with ACTH or corticosterone simulated the effect of stress. After hypophysectomy or adrenalectomy, stress failed to offer the usual protection. [The barbiturates and zoxazolamine appear to have been administered immediately after release of the tourniquet but this is not specifically stated. Allegedly a single injection of corticosterone (50 µg per animal) sufficed to offer protection (H.S.).]

Hexobarbital ← ACTH + Morphine: Rupe et al. E26,910/63*; Bousquet et al. E39,107/64*, F35,073/65*

Pentobarbital ← ACTH + Morphine + Stress: Driever et al. G31,872/65*

Beryllium ←

Ferris et al. B65,475/51: In patients with beryllium granulomatosis of the lung, ACTH was found to be beneficial.

Kennedy et al. B59,278/51: In patients, ACTH exerted beneficial effects upon beryllium granulomatosis and silicosis, presumably as a consequence of its antiphlogistic effect.

Kline et al. B65,488/51: In patients with beryllium granulomatosis, ACTH and cortisone were found to be beneficial.

White et al. B74,079/52: In mice, ACTH had no appreciable effect on the distribution or retention of radioberyllium or on the survival rate following acute intoxication with beryllium sulfate.

Beryllium ← ACTH, Mouse: White et al. B74,079/52*

Bilirubin ← ACTH, Mouse: Catz et al. H14,471/68

Carbon Tetrachloride ←

Patrick C12,967/55: In rats and mice, cortisone or ACTH inhibited the mesenchymal reaction and delayed repair following production of hepatic damage by tannic acid or CCl_4 .

Carcinogens ←

Robertson et al. B88,672/53: In rats, hypophysectomy prevents the production of hepatic cirrhosis and hepatomas by 3'-Me-DAB. The susceptibility to tumorigenesis is restored by ACTH, but not by CON, DOC or testosterone. These hormones likewise failed to prevent carcinogenesis in intact rats.

Currie et al. D48,292/62: In rats, the production of adrenal necrosis by DMBA is prevented by metyrapone, but not significantly influenced by ACTH.

Morii & Huggins D45,369/62: Immature rats are refractory to the production of adrenocortical necrosis by DMBA, unless they are pretreated with ACTH. On the other hand, STH induces no DMBA sensitivity in the immature rat. "The status of susceptibility of the adrenal cortex is correlated with its content of corticosterone."

Morii & Kuwahara G33,213/63: Mice, guinea pigs, hamsters, rabbits, cats and dogs, unlike rats, are not susceptible to the production of adrenal apoplexy by DMBA, and pretreatment with ACTH did not make the adrenals of these species responsive.

Hitachi F67,866/65: In mice, ACTH inhibits the involution of the adrenal cortex produced by MC.

Huggins & Sugiama F44,582/65: In rats, DMBA produces no adrenocortical necrosis if the animals are immature or hypophysectomized. ACTH renders the adrenals of immature rats susceptible to this type of injury.

Morri G34,628/65: Pretreatment with small amounts of ACTH failed to protect the rat against DMBA-induced adrenocortical apoplexy. However, administration of ACTH to young rats or to hypophysectomized adults, which normally do not respond to the corticolytic effect of DMBA, makes them susceptible.

Shirasu et al. F76,819/67: In the rats, hepatoma formation by N-hydroxy-N-2-fluorenlyacetamide (N-OH-FAA) is enhanced by ACTH and STH. Studies with ^{14}C -labeled N-OH-FAA showed "decreased dehydroxylation and deacetylation of N-OH-FAA. The radioactivity bound to liver proteins was

increased, remarkably so in the animals treated with growth hormone."

Ronzoni et al. H18,409/68: In rats, prostatic carcinogenesis induced by the implantation of 20-methylcholanthrene crystals into the prostate is inhibited by ACTH, triiodothyronine and, to a lesser extent, by progesterone and 19-nortestosterone phenylpropionate. Estradiol and cortisone facilitate carcinogenesis, whereas testosterone, orchidectomy and methylthiouracil failed to influence it.

Bird et al. H30,425/70: In rats less than 30 days of age, DMBA or 7-OHM-12-MBA produces no adrenal necrosis unless animals are pretreated with ACTH. However, a single i.v. injection of 7-OHM-12-MBA on the 17th day of gestation causes adrenal necrosis in the embryos as well as in the mothers. Pretreatment with SKF 525-A protected the adrenals both of the embryos and of the mothers.

7,12-Dimethylbenz(*a*)anthracene ← ACTH + Age: *Morii et al. D45,369/62**

9,10-Dimethyl-1,2-benzanthracene ← ACTH: *Currie et al. D48,292/62**

Carcinolytics ←

Andreani et al. C14,628/55: In rats, the different organ changes produced by TEM are unequally influenced by combined treatment with ACTH + cortisone.

Casein ← cf. also *Selye C92,918/61, p. 250.*

Latvalahti B88,191/53: In mice, the amyloidosis produced by repeated s.c. injections of casein is aggravated by ACTH and cortisone but not by DOC or testosterone; orchidectomy facilitates its development.

Peräsalo & Latvalahti C9,661/54: The amyloidosis produced by sodium caseinate s.c. in mice is uninfluenced by DOC and testosterone but aggravated by cortisone, adrenocortical extract and ACTH.

Fanfani & Dini C48,253/57: In mice, combined parenteral administration of casein and ACTH causes necrotic lesions and waxy degeneration in the cardiac muscle but not true amyloidosis.

Cholesterol ← cf. also *Selye G60,083/70, pp. 328, 329, 346.*

Oppenheim & Bruger B74,288/52: In rabbits, cholesterol atheromatosis is diminished by cortisone and to a lesser extent by ACTH.

Tarantino & Natali B71,460/52: In rabbits, ACTH inhibits cholesterol atheromatosis and diminishes the associated hypercholesterolemia.

Cinchophen ←

Rodriguez-Olleros & Galindo C17,868/56: In dogs, induction of gastric ulcers by cinchophen is not significantly affected by ACTH or cortisone.

Diphenylhydantoin ←

Hoyrup & Vinten-Johansen B84,197/52: In patients with acute phenobarbital or diphenylhydantoin poisoning, the use of ACTH is contraindicated as judged by impressions gained from a small series of observations.

Disulfiram ← *c.f. Ethanol****Ethanol*** ←

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and of its metabolites pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Lecoq B79,754/51: In rabbits, injection of disulfiram + ethanol or of Na-pyruvate produces essentially the same syndrome of intoxication, since pyruvic acid is the principal metabolite of ethanol after pretreatment with disulfiram. In either case, ACTH and cortisone offer little, if any, protective effect.

Ethionine ←

Farber & Segalorr D95,996/55: In ovariectomized rats, various testoids and STH protected the liver against fatty infiltration produced by ethionine i.p., whereas cortisone and ACTH aggravated it. Estradiol, DOC and TSH had no effect.

Formaldehyde ← *c.f. Selye B40,000/50, pp. 390, 589.*

Ganglioplegics ←

Brust et al. B57,917/51: In man, "administration of ACTH or cortisone significantly alters the blood pressure and 'TEAC floor'. The responses are independent of sodium retention and indicate that the vascular effects of these drugs are mediated by a humoral mechanism which is potentiated by autonomic blockade." Observations on both normo-

tensive and hypertensive patients showed that "the usual depressor effects of TEAC were ultimately converted to a pressor rise, suggesting that autonomic blockade potentiates the vascular effects of ACTH and cortisone." DOC exhibited no such action.

Brust et al. B58,739/51: In man, the "TEAC floor" rises within 24 hrs after ACTH administration and falls again after discontinuation of hormone treatment. The rise in "TEAC floor" precedes the increase in urinary 17-ketosteroid excretion and precedes or parallels eosinopenia. In patients with uncomplicated essential hypertension blood pressure alterations paralleled the "TEAC floor" changes. "The 'TEAC floor' appears to be a sensitive indicator of the adrenocortical activity produced by ACTH."

Selye G70,448/70: In rats, intoxication with TEA, hexamethonium and pentolinium could be prevented by all of seven glucocorticoids tested. On the other hand, glucocorticoids offered no protection against trimethaphan, mecamylamine, trimethidinium or pempidine. Typical catatotoxic steroids (ethylestrenol, CS-1, spironolactone, norboethrone, oxandrolone) as well as progesterone, DOC and hydroxydione failed to offer significant protection against hexamethonium or TEA. Various stressors (bone fractures, fasting, spinal cord transection and formalin) gave excellent protection against TEA, whereas others (restraint, cold) did not. "Since even large doses of ACTH are ineffective in this respect the anti-TEA effect of stressors cannot be ascribed merely to increased corticoid secretion."

Hexadimethrine ←

Tuchweber et al. D27,884/63: In rats, hypophysectomy prevents the nephrocalcinosis, but aggravates the adrenal necrosis, produced by hexadimethrine. ACTH-treatment of the hypophysectomized rat facilitates the production of nephrocalcinosis, but protects the adrenal. Adrenalectomy prevents this form of nephrocalcinosis even in rats maintained on NaCl or DOC. On the other hand, triamcinolone-treated adrenalectomized rats react to hexadimethrine with strong nephrocalcinosis. Under similar conditions in intact rats, the corticoids did not significantly change the syndrome of hexadimethrine intoxication, except that the anaphylactoid reaction to this compound is inhibited by triamcinolone.

Isoniazid ←

Mrozikiewicz & Strzyzewski G68,152/66; H7,524/67: In the mouse, isoniazid-induced convulsions are facilitated not only by glucocorticoids (cortisol, prednisolone) and ACTH, but also by DOC.

Isoproterenol ← cf. Selye C92,918/61, p. 117.

Lathyrogens ← cf. also Selye G60,083/70, pp. 331, 357.

Selye C25,013/57: The osteolathyrism produced in rats by aminoacetonitrile (AAN) is slightly aggravated by thyroparathyroidectomy, and suppressed by large doses of thyroxine. "An amount of ACTH that more than doubles the weight of the adrenals and causes pronounced thymus atrophy also inhibits the effect of AAN, but fails to prevent it completely. This is all the more noteworthy because comparatively small doses of cortisol can totally prevent such bone lesions. Extensive partial hepatectomy greatly increases the effect of AAN upon the bones."

Selye C31,369/57: In the rat, the osteolathyrism produced by AAN is aggravated by STH, LTH and partial hepatectomy but it is inhibited by ACTH, cortisol or estradiol.

Pyörälä et al. G67,833/59: Dissecting aneurysms of the aorta developed in 40% of immature rats fed *Lathyrus odoratus*. The media was remarkably thickened and the ground substance showed increased metachromasia and PAS reaction. This response was suppressed by cortisone and thyroxine but not by ACTH, TSH or DOC at the doses employed.

van Cauwenberge et al. C78,726/59: In rats, osteolathyrism is inhibited by ACTH and, to a lesser extent, by salicylates and butazolidine.

Glickman et al. E24,104/63: In rats, the dental changes produced by AAN are aggravated following partial hepatectomy and thyroideectomy, reduced by ACTH and almost completely abolished by thyroxine.

Meprobamate ←

Bousquet et al. F35,073/65: In rats with stress produced by applying a tourniquet around one hind limb for 2.5 hrs, the toxicity of hexobarbital, pentobarbital, meprobamate and zoxazolamine was significantly diminished, whereas that of barbital and phenobarbital remained unaffected. Pretreatment with ACTH or corticosterone simulated the effect of stress. After hypophysectomy or adrenalectomy, stress failed to offer the usual protection.

[The barbiturates and zoxazolamine appear to have been administered immediately after release of the tourniquet but this is not specifically stated. Allegedly a single injection of corticosterone (50 µg per animal) sufficed to offer protection (H.S.).]

Mercury ←

Kádas & Zsámely C26,265/56; C49,522/57: The renal damage produced by $HgCl_2$ in the rat is most effectively prevented by testosterone, but, to a lesser extent, also by cortisone, particularly when the latter is given in combination with ACTH.

Morphine ←

Winter & Flataker B62,935/51: In rats, cortisone inhibits the effects of methadone and morphine upon the thermal tail-flick response. Cortisone also increases the excitatory effect of morphine in cats. On the other hand, cortisone synergizes the analgesic antagonist N-allylnormorphine. After spinal cord section, cortisone and ACTH reduce the effect of morphine on the spinal reflex activity in rats (thermal tail-flick response), whereas DOC enhances it.

Adler et al. G79,852/57: In Sprague-Dawley rats given ^{14}C -labeled morphine, the ratio of bound to free morphine is 2–3 times greater in the urine and plasma than in Long-Evans rats. The tissues of adrenalectomized rats of both strains contain higher concentrations of ^{14}C -labeled morphine than do control rats. Plasma bound morphine levels indicate no impairment of morphine conjugation. Vasopressin increases, whereas ACTH decreases morphine sensitivity. Yet both after ACTH and after vasopressin, tissue concentrations of morphine are either reduced or unaffected in marked contrast to the increased values after adrenalectomy. Apparently, the decreased morphine sensitivity induced by ACTH is not reflected by lower brain morphine concentrations.

Sobel et al. C90,836/60: Morphine increases the mortality of guinea pigs exposed to reduced oxygen tension. Prior treatment with cortisone or ACTH protects against this combined treatment.

Markova D47,081/62: Pretreatment with ACTH or cortisone increases the morphine resistance of newborn rats although not quite to the adult level. DOC does not share this effect.

Paroli G12,543/63: In the rat, cortisol and ACTH inhibit the analgesic effect of morphine; dexamethasone and prednisolone (though more active glucocorticoids) do not share this effect.

Lecannelier & Quevedo H8,759/67: In rabbits, the analgesic effect of morphine is reduced by ACTH or cortisol.

Mustard Powder ← cf. *Selye B40,000/50, p. 390.*

Pentylenetetrazol ←

Torda & Wolff B57,149/51: In rats, the convulsions and EEG changes produced by pentylenetetrazol are inhibited by ACTH or cortisone.

Torda & Wolff B69,986/52: In rats, the convulsion-threshold of pentylenetetrazol is raised by ACTH even after hypophysectomy or adrenalectomy. Furthermore, ACTH increases the electric activity of the brain "by a mechanism that is not dependent on the presence of the adrenal cortex."

Boeri C78,610/58: In guinea pigs, cortisone, ACTH and vasopressin aggravate pentylenetetrazol convulsions.

Pentylenetetrazol ← ACTH: *Torda et al. B69,986/52**

Phenyldione ← cf. *Anticoagulants*

Plasmocid ← cf. *Selye C92,918/61, p. 95.*

Polyanetholsulfonate ← cf. *Anticoagulants*

Potassium ←

Collins C17,662/56: Survival after KCl i.p. (referred to as "potassium stress") is diminished after the induction of adrenocortical atrophy by cortisol. Concurrent administration of DOC, aldosterone, adrenocortical extract, corticosterone or ACTH counteracts this effect of cortisol upon K tolerance.

Puromycin Aminonucleoside ←

Wilson et al. C45,755/57: In rats, puromycin aminonucleoside nephrosis is not prevented by cortisone or ACTH.

Pyruvate ←

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are

inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Lecoq B79,754/51: In rabbits, injection of disulfiram + ethanol or of Na-pyruvate produces essentially the same syndrome of intoxication, since pyruvic acid is the principal metabolite of ethanol after pretreatment with disulfiram. In either case, ACTH and cortisone offer little, if any, protective effect.

RES-Blocking Agents ←

Selye B39,702/49: In rats in which an arthritis was produced by intrapodal injection of formalin and India ink, phagocytosis and transport of the carbon particles to the regional lymph nodes are accelerated by ACTH. This is ascribed to glucocorticoid formation and the resulting diminution of the inflammatory barrier at the formalin injection site.

Kennedy et al. B59,278/51: In patients, ACTH exerted beneficial effects upon beryllium granulomatosis and silicosis, presumably as a consequence of its antiphlogistic effect.

Michalová C56,094/58: In rabbits exposed to quartz dust, ACTH diminished the severity of silicosis, but this effect was not manifest in chronic experiments.

Gabbiani et al. G19,450/65: In rats pretreated with ACTH, fluorocortisol or restraint, a single i.v. injection of thorium dextrin (an RES-blocking agent) produces thrombohemorrhagic lesions with necrosis in the adrenals, liver and kidneys. The changes are reminiscent of the Shwartzman-Sanarelli phenomenon.

Göthe H20,085/70: In rats, ACTH accelerates, whereas prednisolone retards, the transport of intratracheally administered quartz dust from the lung to the regional lymphatics.

Silica ← cf. *RES-Blocking Agents*

Tannic Acid ←

Patrick C12,967/55: In rats and mice, cortisone or ACTH inhibited the mesenchymal reaction and delayed repair following production of hepatic damage by tannic acid or CCl_4 .

Tetracaine ←

Zykov H21,879/69: In mice, ACTH, cortisol and DOC failed to influence tetracaine intoxication.

Tetraethylammonium (TEA) ← cf. Ganglionic-Blocking Agents**Thorium Dextrin ← cf. RES-Blocking Agents****Vitamin C ←**

Hyman et al. B53,374/50: "Cortisone and ACTH prolong life and reduce the hemorrhagic manifestations of scurvy in guinea pigs." [In an addendum the authors state that the large doses of ACTH and cortisone used may produce severe toxic effects which overshadow their beneficial actions (H.S.).]

Hyman et al. B57,989/51: In guinea pigs on a vitamin-C deficient diet, ACTH and cortisone ameliorate the manifestations of scurvy.

Vitamin D, DHT ← cf. also Selye G60,083/70, pp. 329, 331.

Selye C27,735/57: The cardiovascular calcification and nephrocalcinosis produced by DHT in rats are aggravated by estradiol, cortisol, ACTH and thyroxine. Conversely, methyltestosterone and STH exert a protective effect.

Thoenes & Schröter C56,987/58: In rats kept on a vitamin-D deficient diet, cortisone tends to inhibit the development of rickets, whereas ACTH does not. DOC actually aggravates vitamin-D deficiency.

Campeanu et al. G21,413/63: In rats, combined treatment with vitamin-D₂ and ACTH produces intense generalized calcinosis. [No mention of controls receiving vitamin-D₂ alone (H.S.).]

Zoxazolamine ←

Bousquet et al. F35,073/65: In rats with stress produced by applying a tourniquet around one hind limb for 2.5 hrs, the toxicity of hexobarbital, pentobarbital, meprobamate and zoxazolamine was significantly diminished, whereas that of barbital and phenobarbital remained unaffected. Pretreatment with ACTH or corticosterone simulated the effect of stress. After hypophysectomy or adrenalectomy, stress failed to offer the usual protection. [The barbiturates and zoxazolamine appear to have been administered immediately after release of the tourniquet but this is not specifically stated. Allegedly a single injection of corticosterone (50 µg per animal) sufficed to offer protection (H.S.).]

Selye G70,480/71: In rats, ACTH inhibited zoxazolamine paralysis and acute DHT-induced soft-tissue calcification but failed to influence poisoning with digitoxin, dioxathion, parathion, nicotine, hexobarbital, progesterone, indomethacin or the infarctoid cardiopathy produced by fluorocortisol + Na₂HPO₄ + corn oil.

Complex Diets ←

ACTH and glucocorticoids inhibit the fatal hepatic necroses which develop in young rats fed diets deficient in sulfur-containing amino acids and vitamin E, as well as in rats kept on diets containing yeast as the only source of protein.

Aterman C35,275/57: The fatal hepatic necrosis which develops in weanling rats fed a diet deficient in sulfur-containing amino acids and vitamin E is inhibited by ACTH and cortisone, but aggravated by thyroid powder feeding. In the case of simultaneous treatment with thyroid and cortisone, the two types of hormones antagonize each other.

Aterman C61,786/58: The hepatic necrosis produced in rats by feeding a diet containing yeast as the only source of protein is inhibited by cortisone, cortisol or ACTH, but not influenced by progesterone, "estrogen," testosterone or DOC. Aldosterone prolongs survival time providing 50 µg or more is administered

daily. Although the author did not report any observations on the effect of aldosterone upon carbohydrate metabolism, he arrived at the conclusion that "these results, therefore, suggest that in the system examined here aldosterone has some 'glucocorticoid' activity and differs significantly from deoxycortone acetate which in doses of 0.5 and 2.5 mgm. daily has been completely ineffective."

Borgman & Haselden H29,947/70: In rabbits kept on a gallstone producing ration, ACTH, thyroid hormones, or cortisone did not inhibit the production of biliary calculi, but several of these hormones inhibited the usually associated hepatic steatosis.

Microorganisms, Parasites and Their Products ←

Bacteria and Vaccines ←. ACTH does not significantly influence the course of infection with *Clostridium tetani* in the mouse or with *Corynebacterium diphtheriae* and leptospirosis in the guinea pig.

Infection with *M. tuberculosis* is aggravated by ACTH in the mouse, guinea pig, rat and rabbit despite a few dissenting claims. In this respect, ACTH imitates the effects of glucocorticoids and, like the latter, it is antagonized by concurrent treatment with STH.

In rats infected with *P. pestis*, ACTH also decreased, whereas STH increased, survival.

Pneumococcal and Rickettsial infections are not very manifestly affected by ACTH in the mouse.

“**Saprophytosis**,” due to proliferation of normally nonpathogenic microorganisms (usually *Corynebacteria*), such as occurs after severe glucocorticoid intoxication, is also induced in rats by heavy overdosage with ACTH. It can be prevented by concurrent treatment with STH.

In guinea pigs and rats, ACTH could not be shown to exert a significant influence upon infection with staphylococci, although cortisone decreased resistance to these organisms.

The effect of ACTH on streptococcal infections varies greatly depending upon experimental conditions.

Viruses ←. ACTH undoubtedly exerts an antipyretic effect in rabbits inoculated with influenza virus as it does in various other forms of infection. In mice and ferrets, ACTH does not significantly influence resistance to influenza. On the other hand, large doses of ACTH increase the susceptibility of mice to lethal infection with various arboviruses. Infection with poliomyelitis is likewise facilitated by ACTH in mice and hamsters, although with some strains of poliomyelitis no definite increase in susceptibility could be obtained by ACTH. In the dog, the growth of equine encephalomyelitis is enhanced by ACTH. This hormone also facilitates the spread of variola virus in sheep and it can reactivate a latent rabies infection in guinea pigs.

Parasites ←. In guinea pigs, ACTH did not significantly influence the course of infestation with *Trichinella spiralis*.

Bacterial Toxins ← cf. also Selye E 5,986/66. In rabbits, pretreatment during 48 hrs with large doses of ACTH or cortisone diminishes the febrile response to *Shigella* endotoxin, whereas 24 hrs of pretreatment with smaller doses of these hormones exerts an opposite effect.

In the mouse, neither ACTH nor cortisone pretreatment raised resistance against the toxins of *R. tsutsugamushi*, *R. prowazeki* or *S. typhosa*. However, under suitable conditions of dosage and timing, mice can allegedly be protected by ACTH or cortisone against fatal intoxication with cholera-vibrio endotoxin, diphtheria toxin and various other endotoxins. The effects of tetanus, Shiga, and meningococcus toxin are not influenced by ACTH in the mouse.

In guinea pigs, neither ACTH nor cortisol improved resistance to diphtheria toxin, but the production of hemorrhages and adrenal necroses by pertussis toxin was enhanced by ACTH.

Rats allegedly cannot be protected against the lethal effects of perfringens toxin by ACTH or glucocorticoids, but the resistance to many endotoxins is undoubtedly increased by these hormones. The hepatic vein thromboses produced in rats on hyperlipemic diets by *S. typhosa* endotoxin are prevented by ACTH, cortisol or prednisolone.

In dogs, ACTH gave no significant protection against endotoxin shock.

In man, the febrile response to killed typhoid bacilli and the reactions to Brucella endotoxin are inhibited by ACTH.

Venoms ←. ACTH has been found to protect various species against fatal doses of the venoms of scorpions, snakes and spiders.

***Bacteria and Vaccines* ←**

***Clostridium Tetani* ←. Massalski & Kulejewska C52,338/57:** In mice, ACTH does not influence experimental tetanus, nor does it alter the actions of tetanus toxin and anti-toxin.

***Corynebacterium Diphtheriae* ←. di Nola et al. C43,232/57:** In guinea pigs, ACTH offered no protection against fatal diphtheria infection.

***Leptospira* ←. Derom & van Hoydonck C17,095/55:** "ACTH and cortisone have not been found to have any favorable effects on the infection of guinea pigs with *Leptospira ictero-haemorragiae*, strain 'Afsnee'."

***Bacillus Piliformis (Tyzzer's disease)* ←. Yamada et al. H24,079/69:** In mice and rats inoculated with *B. piliformis*, pretreatment with ACTH or cortisone greatly enhances susceptibility to Tyzzer's disease.

***Diplococcus Pneumoniae* ←. Kass et al. B69,981/51:** In mice, the final mortality rate after infection with influenza virus or pneumococci is not significantly altered by ACTH or cortisone, although the course of the disease may be modified.

Kass et al. B95,353/54: In mice, resistance to pneumococcal and influenza virus infections is depressed by pretreatment with cortisone or cortisol, but not by ACTH. STH failed to overcome the effect of cortisone and did not increase resistance to infection when given alone.

***Mycobacterium Tuberculosis* ←. Reinmuth & Smith B60,585/51:** In rabbits sensitized by tuberculosis bacilli and subsequently challenged with Old Tuberculin introduced into the trachea, the resulting pneumonia is decreased in severity by pretreatment with ACTH.

Swedberg et al. B58,412/51: In mice, ACTH aggravates the course of experimental tuberculosis.

Lucherini et al. B89,088/53: In guinea pigs, STH inhibits the progress of tuberculosis and counteracts the opposite effect of ACTH.

Cavallero C829/54: Review on the effect of STH, ACTH and cortisone upon various infections, especially in the rat.

Lepri & Fornaro D91,865/54: In rabbits rendered allergic to tuberculosis, the ocular manifestations of topical challenge by tubercle bacilli were variably influenced by ACTH and cortisone.

Youmans & Youmans B95,169/54: In mice, cortisone markedly reduced the survival time after infection with human tubercle bacilli and this effect could not be prevented by STH. Given alone, ACTH, STH and TTH likewise failed to influence the course of the infection.

Donomae et al. C22,935/55: In rabbits infected with human tuberculosis bacilli and reinoculated with the same germs into the lung, ACTH greatly enhances cavity formation.

Greuel & Schäfer E54,859/56: In guinea pigs treated with ACTH, DOC or cortisone, the progress of tuberculosis was proportional to the size of the adrenals, and least severe in animals given cortisol.

Shmelev & Uvarova C53,553/56: Contrary to earlier investigators, the authors found that in guinea pigs and rabbits, ACTH actually increases resistance to tuberculosis.

Wasz-Höckert & Backman C30,700/56: In guinea pigs, the progress of tuberculosis can greatly be enhanced by ACTH, which is useful for the diagnosis of tuberculosis.

Wasz-Höckert & Backman C34,801/56: In guinea pigs, ACTH aggravates the course of tuberculosis. STH in itself is without conspicuous effect, however, "the strongly deterior-

rating effect on tuberculosis produced by ACTH was evidently counteracted by STH when given simultaneously with ACTH."

Batten & McCune C53,554/57: ACTH, cortisol and cortisone greatly reduce the resistance of mice to infection with human tuberculosis.

Florentino D8,379/59: In guinea pigs, ACTH greatly accelerates the progress of tuberculosis. A test for the rapid diagnosis of tuberculosis is based upon this observation.

Renovanz C78,772/59: In guinea pigs, the course of experimental tuberculosis was not markedly influenced by ACTH, tolbutamide derivatives or antithyroid treatment with perchlorates.

Vakilzadeh & Vandiviere E32,626/63: In guinea pigs, the beneficial effect of vaccination against tuberculosis was greatly increased by thyroxine and T₃, but not by cortisone, cortisol or ACTH. None of the hormones altered natural host resistance in nonimmunized guinea pigs.

Wasz-Höckert & McCune E31,145/63: In mice infected with tuberculosis, STH caused an increase in body weight but did not inhibit the development of the infection nor did it counteract the unfavorable effect of ACTH.

Kampioni G33,098/64: In tuberculous guinea pigs, ACTH inhibits the proliferation of the pleural stroma but not the thickening of the mesothelial cells.

Pasteurella Pestis ←. Hayashida C37,366/57: In rats infected with *P. pestis*, ACTH decreased, whereas STH increased, survival.

Rickettsia ←. Jackson & Smadel E52,720/51: Intact mice pretreated with cortisone or ACTH "were given lethal amounts of the toxins of *R. tsutsugamushi*, *R. prowazeki*, or *S. typhosa*. Such animals were as susceptible to the toxins as normal controls. Neither hormone had any therapeutic effect in mice infected with *R. tsutsugamushi*. Furthermore, treated and untreated mice in a terminal phase of infection with *R. tsutsugamushi* were equally susceptible to the toxin of this rickettsia when injected intravenously. In the current experiments the adrenal cortex of normal or infected animals apparently contributed as effectively as possible in the host's response to rickettsial or bacterial toxins and further stimulation was without advantage."

"Saprophytosis" ←. Selye B57,451/51: In rats, "saprophytosis" due to proliferation of normally nonpathogenic microorganisms, such as develop after heavy overdosage with

cortisone or ACTH, can be completely prevented by concurrent administration of STH.

Staphylococcus ←. Debry C30,870/56: Doctor's thesis (176 pp., 578 refs.) on the influence of hormones upon infection. Personal observations on guinea pigs and rats indicate that ACTH, STH and DOC do not significantly affect the course of acute staphylococcus infection, whereas cortisone aggravates it.

Streptococcus ←. Glaser et al. B58,299/50: In mice, neither ACTH nor cortisone exerted a beneficial effect upon streptococcal or pneumococcal infections, indeed they may have aggravated them.

Mogabgab & Thomas B72,457/52: In rabbits, pretreatment with ACTH or cortisone greatly aggravated streptococcal septicemia. DOC had no such effect.

Fazio et al. C34,111/56: In rats, cortisone or ACTH increases survival following streptococcal infection and further enhances the protective effect of penicillin.

Viruses ←

Kass & Finland B54,130/50: In man, the febrile response to i.v. injection of killed typhoid bacilli is reduced by ACTH. A similar antipyretic effect against typhoid bacilli and influenza virus is exerted by ACTH in rabbits.

Loosli et al. B58,316/50: In mice and ferrets, ACTH did not significantly influence air-borne influenza-A infection.

Shwartzman B54,248/50: "ACTH and cortisone in combination or cortisone alone produce a marked acceleration of poliomyelitis infection (strain MEF1) in mice and an extraordinary enhancement of susceptibility to this infection in hamsters giving rise to a violent and uniformly fatal disease. ACTH alone fails to produce this effect possibly due to elaboration of an unknown factor capable of reversing the enhancing effect of cortisone."

Kass et al. B69,981/51: In mice, the final mortality rate after infection with influenza virus or pneumococci is not significantly altered by ACTH or cortisone, although the course of the disease may be modified.

Shwartzman B66,955/51: ACTH and cortisone accelerate poliomyelitis (strain MEF) in mice and hamsters. DOC, progesterone and diethylstilbestrol are ineffective.

Smith et al. B64,635/51: In mice, susceptibility to pneumonia virus (PVM) is not influenced by ACTH but is enhanced by cortisone.

Southam & Babcock B63,662/51: "Large doses of cortisone greatly increased the susceptibility of mice to lethal infection by West Nile, Ilheus, and Bunyamwere viruses. ACTH in massive dosage produced the same effect with West Nile virus. Desoxycorticosterone, testosterone, progesterone, and estradiol in massive doses had no significant effect on these virus infections in mice."

Findlay & Howard B81,142/52: In mice and hamsters, cortisone and ACTH increase susceptibility to polyomyelitis and other virus infections.

Shwartzman B69,778/52: Cortisone, unlike ACTH, greatly increases the susceptibility of Syrian hamsters to i.p. inoculation with strain MEF1 poliomyelitis virus.

Shwartzman & Fisher B69,580/52: In Syrian hamsters, cortisone enhances infection with MEF1 and Lansing strains of poliomyelitis virus. ACTH, DOC, progesterone and stilbestrol are without effect. Earlier literature on the influence of various hormones upon poliomyelitis is reviewed.

Kass et al. B95,353/54: In mice, resistance to pneumococcal and influenza virus infections is depressed by pretreatment with cortisone or cortisol, but not by ACTH. STH failed to overcome the effect of cortisone and did not increase resistance to infection when given alone.

Hurst et al. C94,089/60: Cortisone, ACTH, estradiol, stilbestrol and thyroxine all stimulate the growth of the virus of equine encephalomyelitis in the dog, whereas testosterone and progesterone do not. The hormones which aggravate the infection also counteract the prophylactic effect of mepacrine and abolish the normally greater resistance of the females.

Cilli et al. D12,192/61: In sheep, STH, owing to its prophlogistic effect, delimits the lesions produced by variola virus. ACTH and dexamethasone exert an opposite effect.

Soave D22,275/62: In guinea pigs, latent rabies virus infection can be reactivated by ACTH s.c.

Parasites ←

Luongo et al. B69,505/51: In guinea pigs, ACTH did not significantly influence the course of infestation with *T. spiralis* but appeared to reduce the associated toxic effects.

Sheldon & Bauer D46,962/62: Review on the role of predisposing factors, particularly alloxan diabetes and ACTH-treatment, upon various fungus infections.

Bacterial Toxins ←

RABBIT

Duffy & Morgan B65,399/51: In rabbits the febrile response to *Shigella dysenteriae* endotoxin is diminished following pretreatment during 48 hrs with repeated large doses of ACTH or cortisone. Pretreatment during 24 hrs with smaller doses of these hormones exerts an opposite effect. "This appears to account for the discrepancies in the results previously reported."

Bennett Jr. & Beeson B95,351/53: In rabbits, the febrile response to a single injection of various endotoxins may be decreased, increased or unchanged by treatment with ACTH or cortisone. Acquired resistance to pyrogen fever is abolished by Thorotrust but not by cortisone although both these agents prevent the Shwartzman reaction.

MOUSE

Jackson & Smadel E52,720/51; B77,408/51: Intact mice pretreated with cortisone or ACTH "were given lethal amounts of the toxins of *Rickettsiae tsutsugamushi*, *R. prowazeki*, or *S. typhosa*. Such animals were as susceptible to the toxins as normal controls. Neither hormone had any therapeutic effect in mice infected with *R. tsutsugamushi*. Furthermore, treated and untreated mice in a terminal phase of infection with *R. tsutsugamushi* were equally susceptible to the toxin of this rickettsia when injected intravenously. In the current experiments the adrenal cortex of normal or infected animals apparently contributed as effectively as possible in the host's response to rickettsial or bacterial toxins and further stimulation was without advantage."

Gallut C14,519/55: Mice can be protected against fatal intoxication with cholera *Vibrio* endotoxin by cortisone or ACTH but the degree of protection depends upon dosage and timing.

Massalski & Kulejewska C52,338/57: In mice, ACTH does not influence experimental tetanus, nor does it alter the actions of tetanus toxin and antitoxin.

Nadel et al. D12,681/61: In mice, pretreatment with ACTH offers no protection against endotoxin. Hence, the resistance induced by pretreatment with endotoxin itself cannot be due to mobilization of the pituitary-adrenal axis.

Parant D82,116/62: In mice, resistance to endotoxin is greatly decreased a few hours after adrenalectomy or hypophysectomy. Cortisone protects normal, adrenalectomized,

and hypophysectomized animals against high doses of endotoxin, whereas chlorpromazine is effective only in the presence of both the adrenals and the pituitary. ACTH also protects the hypophysectomized mouse but only if slow absorption is assured.

Skuratova D20,887/62: In mice, resistance against the fatal effect of diphtheria toxin is more markedly increased by STH than by ACTH.

GUINEA PIG

Murray & Brantham B65,414/51: Neither ACTH nor cortisone improved the resistance of guinea pigs to diphtheria toxin or of mice to Shiga and meningococcus toxin.

Okonogi et al. C34,465/56: In guinea pigs the production by pertussis toxin of subcutaneous hemorrhages, pulmonary lesions and adrenal necrosis is enhanced by ACTH.

RAT

Ganley et al. C7,489/55: Rats cannot be protected against the lethal effect of *Clostridium perfringens* toxin by ACTH, adrenocortical extract, cortisol, cortisone or DOC.

Levitin et al. C26,683/56: Cortisol, corticosterone, and cortisone, as well as ACTH protect the rat against endotoxin, whereas DOC does not.

Renaud et al. F74,449/66: In rats kept on a hyperlipemic diet, ACTH, cortisol or prednisolone protected against the production of shock and hepatic vein thromboses by *S. typhosa* lipopolysaccharide. DOC increased

mortality and did not protect against these thromboses.

Dog

Evangelista et al. H16,824/69: Neither ACTH nor stanozolol gave any significant protection against endotoxin shock in dogs.

MAN

Kass & Finland B54,130/50: In man, the febrile response to i.v. injection of killed typhoid bacilli is reduced by ACTH. A similar antipyretic effect against typhoid bacilli and influenza virus is exerted by ACTH in rabbits.

Abernathy & Spink C48,635/58: In man, cortisol or ACTH suppressed or ameliorated reactions to brucella endotoxin.

Venoms ←

Mohammed et al. C7,579/54: Rats can be protected against fatal doses of scorpion toxin by pretreatment with cortisone or ACTH.

Schöttler C10,890/54: In mice and guinea pigs injected with the venom of *Bothrops jararaca* or *Crotalus terrificus* s.c., ACTH, cortisone and cortisol failed to offer protection.

Bettini & Cantore C21,801/55: Comparative studies on the protective effect of ACTH, cortisone and chlorpromazine against lethal poisoning with the venom of the spider *Latrodectus tredecimguttatus*.

Haas G38,758/66: Extensive review on the use of corticoids and ACTH in the treatment of snake bites in man and in animals.

Immune Reactions ←

The immunosuppressive effects of ACTH have been discussed in our previous monographs to which the reader is referred for a more detailed account.

In guinea pigs, ACTH does not strikingly influence anaphylactic shock under usual conditions, yet it may inhibit it if given during 3 days before the challenging reinjection. However, ACTH does clearly diminish tuberculin hypersensitivity although only on diets containing the "cabbage factor" (presumed to be an SH-compound).

The beneficial effect of vaccination against tuberculosis is not significantly altered by ACTH or cortisone in the guinea pig.

In rabbits sensitized to tuberculosis, ACTH tends to, but does not regularly, inhibit the manifestations of subsequent topical challenge.

In rats, ACTH decreases, whereas STH increases, antibody formation against *Pasteurella pestis*. The hemolytic icterus produced by appropriate agglutinin treatment, and the renal damage caused by nephrotoxic serum, can also be inhibited by ACTH.

Hepatic and Renal Lesions ←

Tolerance to temporary **hepatic** vessel ligation is increased by ACTH in the dog. In rats, ACTH (like corticoids) enhances repair and fat deposition in the liver remnant after partial hepatectomy. Various stressors inhibit hepatic regeneration under similar conditions, presumably because the stimulating effect of ACTH and corticoids is overcompensated by the stress itself.

The arterial lesions that develop after bilateral **nephrectomy** in dogs kept on a high-fat diet are prevented by ACTH and cortisone, but also by pregnancy or diethylstilbestrol.

Immune Reactions ← cf. Selye G60,083/70, pp. 328, 329, 347.

GUINEA PIG

Leger et al. A48,766/48: In sensitized guinea pigs, ACTH, given prior to a shock dose of antigen, failed to influence the course of anaphylactic shock.

Dworetzky et al. B52,246/50: In guinea pigs, anaphylactic shock was not significantly influenced by cortisone or ACTH.

Friedlaender & Friedlaender B55,467/50: In guinea pigs, intoxication with histamine (aerosol) and anaphylactic shock (horse serum) were not influenced by pretreatment with ACTH.

Long & Miles D41,973/50: In guinea pigs, moderate thyrotoxicosis produced by two week's treatment with thyroxine increases hypersensitivity to tuberculin, whereas moderate doses of propylthiouracil do not affect it. ACTH and cortisone diminished tuberculin sensitivity. Fourteen days after stopping thyroxine injections, the animals became actually less hypersensitive than the controls. A similar reversal of this effect was noted two weeks after interruption of cortisone or ACTH treatment in that the animals became more hypersensitive than the controls.

Malkiel G71,451/51: In guinea pigs, ACTH and cortisone are without effect on the end results of histamine shock, or of passive or active anaphylaxis.

Long et al. D85,907/51: In guinea pigs, single injections of cortisone or ACTH diminish allergic hypersensitivity on a cabbage diet, but not on a basal diet deficient in the "cabbage factor." The authors conclude "that there is in cabbage a factor which on ingestion leads to the inhibition of the desensitization produced by the metabolism of ascorbic acid in the tissues of the allergic guinea pig; and that the desensitizing action of cortisone or of ACTH

in cabbage-fed animals is indirect, depending on the reversal of the cabbage effect by the hormones. The cabbage factor may possibly be an SH-compound."

Long et al. B60,189/51: In B.C.G.-infected guinea pigs, hypersensitivity to tuberculin is considerably diminished by cortisone or ACTH. This diminution is abolished by pretreatment with propylthiouracil, which alone has no effect upon hypersensitivity. Pretreatment with thyroxine increases tuberculin hypersensitivity but does not block desensitization by ACTH or cortisone. Apparently, thyroxine is necessary for the desensitizing action of ACTH and cortisone.

Long et al. B63,843/51: In guinea pigs, dihydro-ascorbic acid—unlike ascorbic acid—inhibits the tuberculin reaction after infection with B.C.G. vaccine. The desensitizing effect of dihydro-ascorbic acid is not inhibited by thiouracil. Alloxan, like ACTH or cortisone, does not modify desensitization by ascorbic acid on diets deprived of the "cabbage factor;" it desensitizes guinea pigs on a cabbage diet and this desensitization is inhibited by propylthiouracil.

Hoene et al. B68,152/52: In guinea pigs, ACTH given during three days before the challenging reinjection inhibits anaphylactic shock.

Vakilzadeh & Vandiviere E32,626/63: In guinea pigs, the beneficial effect of vaccination against tuberculosis was greatly increased by thyroxine and T3, but not by cortisone, cortisol or ACTH. None of the hormones altered natural host resistance in nonimmunized guinea pigs.

RABBIT

Reinmuth & Smith B60,585/51: In rabbits sensitized by M. tuberculosis and subsequently challenged with Old Tuberculin introduced into the trachea, the resulting pneumonia is

decreased in severity by pretreatment with ACTH.

Lepri & Fornaro D91,865/54: In rabbits rendered allergic to tuberculosis, the ocular manifestations of topical challenge by tubercle bacilli were variably influenced by ACTH and cortisone.

RAT

Hayashida & Li C29,987/57: In rats, ACTH decreases, whereas STH increases, the formation of antibodies against a soluble protein envelope antigen extracted from *P. pestis*.

Vivan & Braito D22,638/62: In rats, the hemolytic icterus produced by appropriate agglutinin treatment can be prevented by concurrent administration of ACTH and glucuronic acid.

Wakim et al. D39,883/63: In rats and dogs, the renal damage produced by nephrotoxic serum can be inhibited by ACTH.

Hepatic and Renal Lesions ←

Hepatic Lesions ←. *Arrigo & Pontremoli B54,373/50:* In rats, ACTH greatly accelerates liver regeneration after partial hepatectomy but does not significantly increase hepatic steatosis.

Raffucci B83,148/53: Dogs tolerate much better repeated temporary rather than continuous occlusion of the hepatic artery and portal vein. ACTH in combination with antibiotics greatly enhances tolerance for noncontinuous-occlusion of the afferent hepatic vessels.

Roberts B97,023/53: In rats, the enhanced repair of the liver following treatment with ACTH or adrenocortical extract is characterized mainly by increased protein deposition in the liver remnant. The usual decline of serum proteins occurring after partial hepatectomy was completely prevented by this treatment.

Hines & Roncoroni C40,870/57: In dogs, the hepatic damage produced by ligature of

all the afferent vessels of the liver during one hour is diminished by ACTH, and survival is improved.

Simek et al. G71,089/68: In intact and even more markedly in adrenalectomized rats, the hepatic accumulation of free fatty acids is increased by cortisol during the early period after partial hepatectomy. ACTH has the same effect but only in the presence of the adrenals.

Simek et al. H13,837/68: Comparative studies on DNA synthesis, fatty acid content, and weight regeneration in the liver remnant of partially hepatectomized rats after treatment with cortisol, ACTH and various stressor agents.

Simek et al. H22,183/68: In rats, the initial increase in liver triglyceride content induced by partial hepatectomy is decreased after adrenalectomy. However, within 24 hrs after the operation, this difference disappears. The effect of adrenalectomy upon the liver triglyceride changes induced by partial hepatectomy can be annulled by epinephrine or cortisone. ACTH augments the immediate rise in liver triglyceride but only in the presence of the adrenals.

Bucher et al. G72,546/69: Review of the humoral factors responsible for hepatic regeneration following partial hepatectomy. Hepatic DNA synthesis is stimulated in intact rats by parabiosis or cross-circulation with partially hepatectomized partners. Furthermore, tiny liver grafts implanted outside the portal area proliferate in response to partial ablation of the parent organ. Various stressors inhibit hepatic regeneration in partially hepatectomized rats, but this effect is not reproduced by ACTH or cortisol. On the other hand, adrenalectomy increases hepatic regeneration.

Renal Lesions ←. *Holman & Jones B93,771/53:* The arterial lesions that develop in dogs kept on a standard high-fat diet upon subsequent nephrectomy are prevented by pregnancy, cortisone, ACTH or diethylstilbestrol.

Varia ←

Ionizing Rays ←. Resistance to total body X-irradiation is not significantly influenced by ACTH in the mouse, rat or man, although some investigators claim to have obtained moderate protection by ACTH at least in rats.

Hypoxia and Hyperoxygenation ←. In mice and man, resistance to hypoxia is increased by ACTH, whereas in guinea pigs, allegedly tolerance to both hypoxia and hyperoxygenation is diminished by this hormone. It has been claimed, however,

that in guinea pigs, whose resistance to hypoxia is increased by morphine, prior treatment with ACTH or cortisone protects against this combined treatment.

Temperature Variations ←. According to some investigators, the survival time of severely burned rats is not influenced by ACTH; others claim that the hormone prolongs survival. Cold tolerance is allegedly increased by prolonged ACTH pretreatment in this species.

In mice, ACTH does not protect against the fatal effects of burns, but allegedly pretreatment with ACTH increases resistance to cold.

Other Stressors ←. In rats, ACTH (like STH) and glucocorticoids decrease the EST.

ACTH allegedly aggravates the calcifying arteriosclerosis that tends to develop in rats exposed to the stress of repeated breeding.

An improvement in muscular performance (swimming) could be induced in rats by ACTH, but only at a critical temperature.

The resistance to trauma (Noble-Collip drum, tourniquet shock) is moderately enhanced by ACTH pretreatment in the rat.

In trout, salinity tolerance is not affected by ACTH, although it can be significantly altered by several other hormones.

Ionizing Rays ←

Smith et al. B47,642/50: In mice, neither ACTH nor cortisone increased survival following X-irradiation.

Rigat C10,747/55: Review (46 pp., 67 refs.) of the literature concerning the effect of hormones upon X-irradiation, with special reference to ACTH, STH, vasopressin, epinephrine, cortisone, DOC, testosterone, estradiol, progesterone, and thyroxine.

Taber C10,417/55: In man, ACTH increases resistance to radiation sickness.

Kedrova & Krehkova G71,665/59: In rats, ACTH offers some protection against lethal X-irradiation. Although cysteine has a similar effect by itself, it actually blocks the protective effect of ACTH.

Kandror E27,416/63: Review of the literature on the effect of corticoids and ACTH upon total body X-irradiation, especially in connection with the physiopathology of stress.

Orlova et al. G22,562/63: In rats, long-acting ACTH preparations offer protection against total body X-irradiation.

Trinci G45,713/66: In rats, resistance to X-irradiation was not markedly affected by pretreatment with ACTH.

Cittadini et al. G76,028/70: In X-irradiated mice, the formation of hemopoietic islets in the spleen is inhibited by dexamethasone, ACTH or the stress of exposure to cold.

Hypoxia and Hyperoxygenation ←

Frawley et al. B57,930/51: In man, both cortisone and ACTH improve high altitude tolerance.

Parkes B63,024/51: In mice, resistance to anoxia is increased by posterior lobe extract as well as by ACTH preparations containing posterior lobe principles.

Grognot & Senelar C41,294/57: In rats and guinea pigs, the pulmonary inflammation induced by inhalation of pure oxygen at normal barometric pressure is aggravated by ACTH or histamine.

Volterrani C64,384/57: In guinea pigs, tolerance to hypoxia is decreased by cortisone but increased by ACTH pretreatment.

Sobel et al. C90,836/60: Morphine increases the mortality of guinea pigs exposed to reduced oxygen tension. Prior treatment with cortisone or ACTH protects against this combined treatment.

Temperature Variations ←

Neal et al. B80,371/52: The survival time of severely burned rats is not influenced by cortisone or ACTH, whereas DOC administered before the burn offers considerable protection.

Schöttler C8,455/55: Neither ACTH nor cortisone protect the mouse against the fatal

effects of severe scalding; in fact, cortisone increases mortality.

Kirsteins C41,958/56: Short term cortisone or ACTH administration to rats did not significantly influence cold tolerance, whereas long-term intermittent cortisone administration prior to exposure to cold definitely raised tolerance in this respect.

Koch et al. C33,922/57: In rats, ACTH, unlike STH, prolongs survival following severe burns.

Garrido C77,562/59: In intact rats, prednisone and ACTH increased resistance to cold.

Hale & Mefferd Jr. C79,669/59: In rats exposed to cold and various other stressors, pretreatment with "ACTH had a 'restraining' influence on nonspecific metabolic responses."

Yang & Lissak C77,913/59: In rats, the improvement of muscular performance (swimming) induced by ACTH is fully evident only at a critical temperature.

Knigge C97,819/60: Review on the neuroendocrine mechanisms influencing ACTH and TTH secretion, particularly during adaptation to cold.

Agarkov et al. D40,496/62: In intact rats, cortisone raises resistance to heat, whereas ACTH does not.

Araki G11,847/63: Pretreatment with ACTH or cortisol raises the resistance of intact mice to exposure to cold. Nicotinamide has a similar effect which is ascribed to stimulation of the pituitary-adrenal system.

Other Stressors ←

Electric Stimuli ←. *Minz & Domino B81,852/53:* In rats, small doses of epinephrine or norepinephrine prolong the duration of electrically-induced seizures. Since glucose, ACTH and cortisone failed to prolong seizure duration, it is unlikely that epinephrine acts by release of these substances. Histamine depressed the cortical response to electroshock.

Woodbury B98,594/54: Review (42 pp., 90 refs.) on the "Effect of Hormones on Brain Excitability and Electrolytes." In the rat, the EST is increased by DOC and decreased by cortisone and cortisol. ACTH and 11-dehydro-

corticosterone, given chronically, partially antagonize the effect of cortisone.

Rosenblum C5,974/55: In rats, "ACTH and cortisone acetate in combination with vasopressin each produced a greater fall in EST than was produced by vasopressin alone. In contrast, STH in combination with vasopressin prevented the fall induced by vasopressin alone and produced its usual elevation in the EST."

Trauma ←. *Noble & Collip A56,107/42:* Adrenocortical extract and DOC greatly increase the resistance of adrenalectomized rats to the trauma of the Noble-Collip drum. In intact rats, "cortin" and DOC as well as ACTH induce only a slight increase in resistance under similar circumstances. "From a practical viewpoint the effects of adrenal preparations on this type of shock have been disappointing."

Kulagin D236/61: In rats with a crush syndrome produced by clamping a thigh, survival was increased by ACTH, cortisone and cortisol, whereas DOC aggravated the condition by increasing edema in the injured area.

Khrabrova D33,557/62: Both ACTH and cortisone prolong survival following traumatic shock in the cat.

Muscular Work ←. *Yang & Lissak C77,913/59:* In rats, the improvement of muscular performance (swimming) induced by ACTH is fully evident only at a critical temperature.

Osmosis ←. *Smith C46,496/56:* In brown trout, thyroxine raises, whereas thiourea and thiouracil reduce, salinity tolerance. Anterior pituitary extracts and STH likewise raise salinity tolerance, whereas posterior lobe extracts, testosterone, gonadotrophin, TTH and ACTH have no effect.

Tumors ←. *Glenn et al. G70,204/60:* Review (48 pp., 11 refs.) on the effect of various steroids, ACTH, GTH, ovariectomy, and adrenalectomy upon the development of C3H mammary carcinoma transplants in mice and fibroadenomas in rats.

Repeated Breeding ← cf. Selye C50,810/58, p. 82; C92,918/61, p. 230; G60, 083/70, pp. 328, 330.

Hepatic Enzymes ←

In the rat, ACTH increases the TPO and TKT activity of the liver even without concurrent treatment with the corresponding substrates. In this respect, ACTH imitates the actions of glucocorticoids and of various stressors which cause ACTH and glucocorticoid secretion.

ACTH also increases hepatic GPT activity even in hypophysectomized but not in adrenalectomized rats. Presumably this effect is likewise mediated through the adrenal cortex.

Observations with the use of marked cholesterol in the rat showed that ACTH decreases the rate of cholesterol palmitate and oleate synthesis.

TPO, TKT ←

Geschwind & Li B95,517/53: Hypophysectomy does not abolish (and perhaps even increases) the resting TPO activity of the rat liver. However, in hypophysectomized animals, the ability to induce this enzyme by tryptophan injection is gradually diminishing during the first 14 post-operative days. Treatment with ACTH enhances the formation of this adaptive enzyme system (measured by kynurenin formation) even without treatment with tryptophan.

Knox & Auerbach E76,825/55: ACTH increases TPO activity of the liver in the rat.

Maickel & Brodie C83,071/60: TPO in rat liver is increased by ACTH, cortisone, or cortisol, as well as by various stressor agents and barbiturates. Hypophysectomy prevents the effect of stressors and barbiturates, suggesting that the latter act through the pituitary-adrenal system.

Knox G51,969/62: Review on the effect of stress upon hepatic TPO production. In adrenalectomized animals, only tryptophan of a series of analogues induces this enzyme, whereas, in intact rats, various stressors, ACTH, cortisone, cortisol and corticosterone (but not DOC) do so. "The recognition of the adrenal hormone-induced adaptation of the tryptophan pyrrolase has provided the unified explanation for a large number of different stressful stimuli which increase the enzyme level." Tryptophan pyrrolase is absent from the liver of newborn rabbits and in them, this enzyme cannot be induced by cortisol. Tyrosine transaminase induction is regulated in a very similar manner.

GPT ←

Rosen et al. C71,414/59: Marked increases in GPT activity were observed in the livers of rats given cortisol, cortisone, 9 α -fluorocorti-

sol, prednisone, 6 α -methylprednisolone, 9 α -fluoro-21-desoxy-6 α -methylprednisolone or ACTH, whereas two nonglucocorticoid cortisol derivatives, 11-epicortisol and 9 α -methoxy-cortisol were inactive. STH, testosterone and insulin caused no significant change in GPT by themselves nor did they modify the action of cortisol.

Harding et al. D14,355/61: In the rat, pre-treatment with DOC depresses the hepatic GPT activity. A similar depression is obtained by adrenalectomy, but this is not further aggravated by concurrent treatment with DOC. ACTH increases GPT activity in hypophysectomized, but not in adrenalectomized, animals. In hypophysectomized rats, DOC fails to lower alanine transaminase, nor does it alter the response of this enzyme to ACTH. "The inhibitory effect of DOC on alanine transaminase activity appears to be due to suppression of ACTH release by the pituitary."

Cholesterolase ←

Schweppé & Jungmann H15,978/69: Observations on the metabolism of marked cholesterol added together with various hormones to hepatic microsomes of the rat led to the conclusion that "1) cholesterol palmitate and oleate were synthesized most rapidly; 2) at high concentrations, testosterone decreased the formation of all esters but at lower dose levels, testosterone increased the synthesis of cholesterol oleate and palmitate; 3) estradiol caused a two-fold increase in cholesterol oleate formation; 4) ACTH decreased the synthesis rate of cholesterol palmitate and oleate; 5) insulin had a significant inhibitory effect on cholesterol linoleate; 6) epinephrine had little significant effect at the dose level used; and 7) L-thyroxine increased the synthesis of all cholesterol esters."

← SOMATOTROPHIC HORMONE (STH)

Steroids ←

The effects of corticoids can be modified by STH in many respects. In rats sensitized by uninephrectomy + NaCl, STH produces a hyalinosis syndrome with

malignant hypertension, similar to that elicited by mineralocorticoids. The corresponding action of DOC is aggravated by STH. Adrenalectomy or pretreatment with cortisone (in doses sufficient to produce adrenocortical atrophy) inhibits the production of hyalinosis by STH. It is assumed that STH induces malignant hypertension by increasing the production or the effect of mineralocorticoids.

Glucocorticoid overdosage symptoms (catabolism, splenic and thymic atrophy, "saprophytosis") are prevented in rats by simultaneous administration of STH. On the other hand, a synergism between STH and mineralocorticoids (DOC, aldosterone) has been demonstrated (in both intact and adrenalectomized rats) as judged by their effects upon many target organs.

The inhibition of growth by **folliculoids** (e.g., stilbestrol) can be blocked in rats by concurrent STH administration, but this conjoint treatment results in particularly severe osteosclerosis.

Corticoids ←

Selye B53,940/51: In uninephrectomized NaCl-treated rats, the hyalinosis syndrome produced by DOC is aggravated by STH; indeed, STH alone can engender malignant hypertensive disease. These effects of STH are inhibited by cortisone. Apparently STH increases mineralocorticoid production by the adrenals (unless these are rendered atrophic by cortisone) and/or sensitizes the peripheral tissue to mineralocorticoids.

Selye B65,065/52: In rats, large doses of cortisone permit the proliferation of normally saprophytic organisms which cause multiple abscesses and hepatic necroses (the "saprophytosis syndrome"). All these changes can be prevented by simultaneous treatment with STH.

Horava & Selye B70,249/53: In rats, heavy overdosage with cortisol produces intense catabolism with atrophy of the adrenals, thymus and spleen, as well as pulmonary "saprophytosis." Concurrent administration of STH inhibits the body weight loss and the saprophytosis, but not adrenal and thymus atrophy. The renal glomerular changes induced by cortisol intoxication are actually aggravated by STH.

Ducommun & Ducommun B70,251/53: In rats, saprophytosis produced by heavy overdosage with cortisone is inhibited by concurrent administration of STH. This "anti-infectious effect of STH" is much less evident after adrenalectomy. DOC, testosterone, and estradiol alone or in combination failed to duplicate the anti-infectious action of STH in cortisone-treated rats.

Selye & Bois C1,718/55: In intact and in adrenalectomized rats, a synergism between mineralocorticoids (DOC, aldosterone) and STH was evident in their effects upon many target organs.

Bavetta et al. D29,064/62: In the rat, "growth hormone, methyl testosterone or stilbestrol, when given alone or in combination were not able to counteract the inhibitory effects of 6-methyl prednisolone on body weight and collagen synthesis at the site of subcutaneously implanted polyvinyl sponges."

Folliculoids ←

Selye B70,245/53: In rats, the inhibition of growth produced by a folliculoid substance, such as stilbestrol, can be inhibited by STH, but this conjoint treatment results in severe osteosclerosis.

Drugs ←

STH conspicuously influences the toxicity of only a few drugs. For example in rats, it tends to aggravate the production of hepatic sclerosis by CCl_4 while diminishing parenchymal injury.

In rats, hepatoma formation by certain carcinogens is enhanced both by STH and by ACTH. Studies with ^{14}C -labeled N-OH-FAA showed decreased dehydroxylation

and deacetylation of the carcinogens as well as increased binding of radioactivity to liver proteins in animals treated with STH.

Female rats are much more resistant than males to the induction of cardiovascular and renal lesions by choline deficient diets. However, STH sensitizes the female to the production of these changes by choline deficiency, perhaps because the increased growth rate accelerates the exhaustion of choline stores.

The bone changes produced by various **lathyrogens** are very considerably aggravated by STH. Conversely, hypophysectomy prevents these changes, and substitution with STH in doses just sufficient to maintain normal growth restores the susceptibility of the skeleton to the production of lathyrism. It was concluded that the normal STH secretion of the hypophysis decisively influences the development of this bone disease. The lathyrism-enhancing effect of STH is not mediated through the adrenals, since it is evident even after bilateral adrenalectomy.

The cardiac infarcts produced by coronary artery ligature in the rat tend to develop into rupturing cardiac aneurysms under the influence of the lathyrogen, AAN. This effect is not significantly altered by STH. Similarly, STH fails to influence the hemorrhagic tendency induced by lathyrogens such as AAN. Hence, there does not appear to be any close relationship between the effect of STH upon the skeletal and the cardiovascular manifestations of lathyrism. Furthermore, the hormones presumably act directly upon the responsiveness of individual target organs, and not by altering the metabolism of the lathyrogens.

In the rat, the catabolism produced by **nitrogen mustard** is not prevented, and even tends to be aggravated, by STH alone; yet, excellent protection is obtained by combined treatment with STH and antibiotics.

On the other hand, the growth stimulating effect of STH is greatly diminished in rats given diets deficient in **phenylalanine**, **tryptophan**, or **tyrosine**.

In rats kept on a **vitamin-A** deficient diet, STH fails to promote growth, and actually precipitates the manifestations of avitaminosis. On the other hand, the intense catabolism and bone absorption produced in rats by vitamin-A overdosage are prevented by STH.

The cardiovascular calcification engendered by **vitamin-D** derivatives, such as **DHT**, is somewhat diminished, but not prevented by STH, although the associated catabolism is markedly inhibited.

Acrylonitrile ←

Szabó & Selye G79,010/71: In rats, pretreatment with ACTH (but not with STH) prevents the production of adrenal apoplexy by acrylonitrile. Hypophysectomy protects against adrenal apoplexy, but not against mortality under similar conditions.

Aminopyrine Barbiturates ←

Wilson H34,926/71: In rats, implants of mammatropic tumor (which secretes STH, ACTH and LTH) decreased the hepatic metabolism of hexobarbital and aminopyrine. Simi-

lar but much less pronounced changes were observed in rats bearing very large Walker tumors.

Anaphylactoidogenic Agents ←

Higginbotham & Dougherty C44,529/57: In mice, ACTH increased the toxicity of polymyxin B; STH and TTH had no effect upon it.

Anticoagulants ←

van Cauwenberge & Jaques C58,521/58: A dose of bishydroxycoumarin (Dicoumarol) well tolerated by otherwise untreated rabbits,

causes death with widespread hemorrhage when given together with ACTH. The hemorrhagic tendency induced by coumarol was not accentuated by STH, cortisone or DOC.

van Cauwenberge & Jaques C72,748/59: The "hemorrhagic death syndrome" produced by Dicoumarol treatment in rats simultaneously exposed to various stressors can be reproduced by the administration of ACTH, STH, or DOC, instead of stressors. Dicoumarol + cortisol or cortisone did not reproduce this syndrome.

Carbon Tetrachloride ←

Campanacci Jr. et al. C20,086/56: In rats, small doses of STH increase the hepatic sclerosis produced by CCl_4 , whereas at high dose levels, the hormone aggravates parenchymal degeneration, but inhibits sclerosis.

Post et al. C40,180/57: In rats, the hepatic injury produced by CCl_4 is diminished by STH.

Furukawa F71,711/65: In rats, hepatic steatosis produced by CCl_4 is inhibited by adrenalectomy and, to some extent, also by hypophysectomy. The effect of CCl_4 after adrenalectomy is restored by corticoids, but not by epinephrine which only increases the action of the former. STH does not counteract the effect of hypophysectomy. Alloxan diabetes inhibits CCl_4 -induced hepatic lipidosis.

Carcinogens ←

Reid B93,930/54: Review (18 pp., 181 refs.) on the effect of STH and corticoids upon carcinogen-induced and transplantable neoplasms.

Shirasu et al. F76,819/67: In the rats, hepatoma formation by N-hydroxy-N-2-Fluorenlyacetamide (N-OH-FAA) is enhanced by ACTH and STH. Studies with ^{14}C -labeled N-OH-FAA showed "decreased dehydroxylation and deacetylation of N-OH-FAA. The radioactivity bound to liver proteins was increased, remarkably so in the animals treated with growth hormone."

7,12-Dimethylbenz(*a*)anthracene ←
STH + Age: Morii et al. D45,369/62*

Choline ←

Wilgram & Hartcroft C14,392/55: Female rats are much more resistant than males to the production of cardiovascular lesions by choline deficiency. However, simultaneous administration of "androgens" (kind not specified) and

STH sensitizes the female to the induction of these lesions by hypolipotrophic rations.

Wilgram et al. C15,960/56: Both STH and testosterone aggravate the renal and cardiovascular lesions characteristic of choline deficiency in the rat.

Wilgram C84,322/59: In rats, STH increases the severity of the cardiovascular lesions produced by choline deficiency.

Aterman D15,536/61: In male weanling rats, the hepatic necrosis induced by feeding a diet containing yeast as the sole source of protein is greatly accelerated by partial hepatectomy or treatment with STH.

Chlorpromazine ←

Epple et al. F76,569/66: In toads, the hypothermic action of chlorpromazine and ethanol is diminished by STH.

Ethanol ←

Epple et al. F76,569/66: In toads, the hypothermic action of chlorpromazine and ethanol is diminished by STH.

Ethionine ←

Farber & Segaloff D95,996/55: In ovariectomized rats, various testoids and STH protected the liver against fatty infiltration produced by ethionine i.p., whereas cortisone and ACTH aggravated it. Estradiol, DOC, and TSH had no effect.

Lathyrogens ← cf. also Selye C92,918/61, p. 137.

Selye & Bois C18,280/56: In rats, the osteolathyrism produced by lathyrus odoratus seeds is aggravated by STH and inhibited by cortisol. Combined treatment with DOC + uninephrectomy + NaCl resulted in dissecting aneurysms of the aorta. Very small doses of thyroxine or estradiol were without effect upon this form of lathyrism.

Dasler C36,068/57: Brief mention of unpublished observations indicating that in rats, osteolathyrism produced by APN is not inhibited by cortisone or thyroxine, but aggravated by STH.

Selye C25,910/57: In rats, the osteolathyrism produced by moderate doses of AAN is greatly aggravated by STH.

Selye C31,369/57: In the rat, the osteolathyrism produced by AAN is aggravated by STH, LTH, and partial hepatectomy, but it is inhibited by ACTH, cortisol, or estradiol.

Selye C31,790/57: In rats, osteolathyrism produced by AAN is inhibited by thyroxine,

cortisol, and estradiol, but aggravated by STH even after adrenalectomy.

Selye & Bois C22,712/57: In rats, osteolathyrism (produced by AAN) is inhibited by cortisol and augmented by STH. The combination of STH and AAN enhances the development of polyarthritis in the small joints of the extremities. DOC facilitates the production of aortic aneurysms by AAN.

Selye & Bois C23,297/57: In rats, STH greatly aggravates the osteolathyrism produced by AAN.

Selye & Ventura C27,684/57: In rats, hypophysectomy greatly diminished the development of the osteolathyrism normally produced by AAN, but STH aggravated these bone lesions even more in the absence than in the presence of the pituitary. It is concluded that the normal hormonal secretion of the hypophysis exerts a decisive influence on the development of osteolathyrism.

Selye & Cantin C88,878/61: In rats, the osteolathyrism produced by AAN is inhibited by thyroxine and cortisol, but aggravated by STH. The cardiac infarcts elicited in rats by ligation of the descending branch of the left coronary artery are often transformed into rupturing cardiac aneurysms under the influence of AAN. The incidence of these cardiac ruptures is augmented by cortisol and DOC, but not significantly influenced by thyroxine and STH. Evidently, there is no direct relationship between the skeletal and the cardiac lesions under these circumstances.

Aschkenasy D30,892/62: In rats, lathyrism produced by AAN is aggravated by adrenalectomy and, in the absence of the adrenals, the usual antilathyrism effect of cortisone is no longer demonstrable; in fact the glucocorticoid facilitates the production of hernias. STH aggravates the osteolathyrism, but not the induction of hemorrhages by AAN.

Nitrogen Mustard ←

Mitchell & Girerd B82,866/53: In rats, the catabolism and mortality produced by nitrogen mustard is actually aggravated by STH alone, and only slightly inhibited by antibiotics; STH + antibiotics offer excellent protection.

Phenylalanine ←

Scott & Dynes C53,564/57: In rats on a phenylalanine- and tyrosine-deficient diet, STH caused less stimulation of the epiphyseal growth plate than in pair-fed animals.

Reiss et al. F81,632/66: In rabbits given large amounts of phenylalanine, the blood and tissue concentration of this compound could be reduced by pretreatment with norbolethone decanoate or STH.

Plasmocid ← cf. *Selye C92,918/61*, p. 95.

Tryptophan ←

Bavetta et al. C17,656/56: In rats on a tryptophan-deficient diet, STH failed to increase body weight, but it did stimulate endochondral osteogenesis and dentin formation.

Tyrosine ←

Scott & Dynes C53,564/57: In rats on a phenylalanine- and tyrosine-deficient diet, STH caused less stimulation of the epiphyseal growth plate than in pair-fed animals.

Vitamin A ←

Ershoff & Deuel Jr. B14,516/45: In vitamin-A deficient rats, STH fails to promote growth, and actually shortens survival by the precipitation of acute vitamin-A deficiency symptoms.

Selye C36,050/57: In rats, the intense osteoclastic bone absorption produced by vitamin-A overdosage can be prevented by STH. Although the luteotropic hormone (LTH) shares many of the actions of STH, it cannot substitute for the latter in counteracting vitamin-A intoxication, cf. Fig. 21.

Bavetta C60,277/58: In rats, STH failed to increase body weight on a vitamin-A deficient diet, but endochondral ossification was enhanced, and dentin formation stimulated. "The suggestion is made that impaired chondrogenic and osteogenic activity in vitamin A-depleted rats is due, at least in part, to an inadequate production or secretion of growth hormone."

Bottiglioni et al. C70,889/59: In rats, the atrophy of the skeletal musculature and the decreased metachromasia of the aortic wall produced by vitamin-A deficiency are aggravated by STH.

Vitamin C ←

McGraw C68,484/59; C80,136/59: Doctor's thesis describing numerous experiments on the effect of adrenalectomy, cortisone, thyroxine, thyroidectomy, thiourea, and STH upon scorbutic guinea pigs, with special emphasis upon changes in capillary resistance and cold tolerance.

Vitamin D, DHT ← cf. also *Selye G60,083/70*, pp. 331, 333.

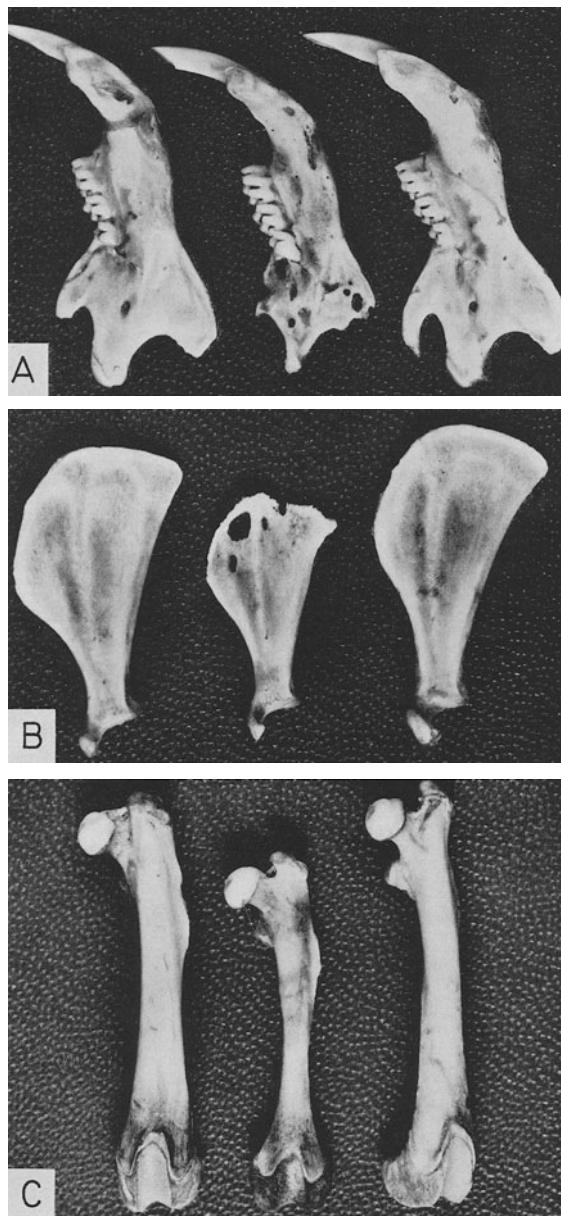


Fig. 21. Prevention of vitamin-A induced skeletal lesions by STH. A: Mandible of normal (left), vitamin-A treated (middle) and vitamin-A + STH-treated rats. Note that hypervitaminosis A resulted in several perforations within the flat part of the mandible and in absorption of the coronoid and condyloid processes with disappearance of the angle of the jaw. All these changes have been completely prevented by STH. B: Scapula of normal (left), vitamin-A treated (middle) and vitamin A+STH-treated rat. Again, the resorption of bone normally produced by vitamin A has been prevented by STH. C: Femur of a normal (left), a vitamin-A treated (middle) and vitamin A + STH-treated rat. The antagonism between STH and vitamin-A is clearly visible. [Selye C36,050/57. Courtesy of J. Endocrin.]

Selye C27,735/57: The cardiovascular calcification and nephrocalcinosis produced by DHT in rats are aggravated by estradiol, cortisol, ACTH, and thyroxine. Conversely, methyltestosterone and STH exert a protective effect.

Zinc ←

Prasad et al. G64,823/69: In rats kept on a zinc-deficient diet, STH failed to promote growth.

Varia ←

Selye G70,480/71: In rats, STH offered some protection against progesterone anesthesia but did not alter the syndrome of intoxication with digitoxin, dioxathion parathion, nicotine, hexobarbital, zoxazolamine, indomethacin, acute DHT intoxication or the myocardial necroses produced by fluorocortisol + Na₂HPO₄ + corn oil.

Diet ← cf. *Selye G60,083/70, pp. 331, 333.*

Microorganisms, Parasites and Their Products ←

As previously stated, STH counteracts the facilitating effect of glucocorticoids and of ACTH upon the spread of various infections. This has first been demonstrated for the "saprophytosis" that develops in rats as a consequence of the proliferation of normally saprophytic organisms. STH also exerts a beneficial effect upon resistance of mice to **pneumococci** and **typhoid bacilli**, and of rats to **P. pestis**. On the other hand, STH does not appear to modify the course of **staphylococcus** infection in rabbits.

The most extensive studies on the effect of STH have been conducted in connection with experimental **tuberculosis**. In the rat, there appears to exist a definite antagonism between the resistance-decreasing action of ACTH and glucocorticoids on the one hand and the protection offered by STH on the other. This has been confirmed by some investigators in guinea pigs and mice; indeed, it has been claimed that STH exerts a favorable effect even in human tuberculosis. However, many of the reports are contradictory, probably owing to genetic differences in the strains of the bacteria and hosts, as well as to variations in the potency and immunologic compatibility of the STH preparations employed.

In mice, the proliferation of influenza **virus** is accelerated by STH, perhaps as a consequence of enhanced protein synthesis in general. The detrimental effect of ACTH and cortisone upon the course of influenza virus infection in mice is not overcome by STH. However, the increase in the sensitivity of the mouse to infection with MHV-3 hepatitis virus, induced by different glucocorticoids, is largely counteracted by STH. In sheep, STH tends to delimit the lesions produced by variola virus, but in mice its effect upon vaccinia virus is not very pronounced.

In mice, STH retards the development of infection with parasites, **Plasmodium berghei**, and in frogs, it inhibits infection with **Trypanosoma inopinatum**.

The moniliasis produced by **Candida albicans** in mice is aggravated by cortisone and this deleterious effect is counteracted by STH.

STH offers no protection against **typhoid endotoxin** in the mouse, but resistance against diphtheria toxin appears to be increased.

Bacteria and Vaccines ←

Corynebacteria ← cf. *Selye C92,918/61, p. 233.*

"**Endotheliomyelosis**" ← cf. *Selye C92,918/61, p. 241.*

"**Saprophytosis**" ←. *Selye B57,451/51:* In rats, "saprophytosis" due to proliferation of normally nonpathogenic microorganisms, such as develops after heavy overdosage with cortisone or ACTH, can be completely prevented by concurrent administration of STH.

Selye B65,065/52: In rats, large doses of cortisone permit the proliferation of normally saprophytic organisms which cause multiple abscesses and hepatic necroses (the "saprophytic syndrome"). All these changes can be prevented by simultaneous treatment with STH.

Pneumococcus ←. *Kass et al. B95,353/54:* In mice, resistance to pneumococcal and influenza virus infections is depressed by pretreatment with cortisone or cortisol, but not by ACTH. STH failed to overcome the effect of cortisone and did not increase resistance to infection when given alone.

Meier & Neipp C37,215/56: In mice, the chemotherapeutic action of sulfonamides against resistant Type III pneumococci is increased by various gonadotrophic and STH preparations. However, certain bacterial polysaccharide fractions possess a similar effect, and hence, the latter is presumably not dependent upon the specific actions of the hormone preparations.

Staphylococcus ←. *Debry C30,870/56:* Doctor's thesis (176 pp., 578 refs.) on the influence of hormones upon infection. Personal observations on guinea pigs and rats indicate that ACTH, STH, and DOC do not significantly affect the course of acute staphylococcus infection, whereas cortisone aggravates it.

Herbeuval et al. C55,675/58: In rabbits, STH does not modify the course of staphylococcus infection.

Typhoid Bacilli ←. *Jude et al. C16,220/55:* In mice, STH pretreatment protects against subsequent infection with typhoid bacilli. The protection is ascribed to improved antibody formation and phagocytosis. STH offers no protection against typhoid endotoxin.

Pasteurella Pestis ←. *Hayashida C37,366/57:* In rats infected with P. pestis, ACTH decreased, whereas STH increased survival.

Mycobacterium Tuberculosis ←. *Lemonde et al. B70,248/52:* The rat which is naturally resistant to human M. tuberculosis can be made sensitive to this infection by pretreatment with cortisone. This sensitivity is in turn abolished by concurrent treatment with STH. Mice which are naturally sensitive to tuberculosis can also be protected by STH.

Lucherini et al. B89,088/53: In guinea pigs, STH inhibits the progress of tuberculosis and counteracts the opposite effect of ACTH.

Chirico et al. C5,040/54: In guinea pigs, the late pulmonary manifestations of tuberculosis are enhanced by STH and the fibrotic healing processes are improved. The effects of the

hormone are ascribed to a stimulation of mesenchymal defense reactions.

Lemonde C310/54: Doctor's thesis (186 pp., 564 refs.) on humoral factors influencing infections, with special reference to the effect of STH and cortisone upon experimental tuberculosis.

Youmans & Youmans B95,169/54: In mice, cortisone markedly reduced the survival time after infection with human tubercle bacilli, and this effect could not be prevented by STH. Given alone, ACTH, STH, and TTH likewise failed to influence the course of the infection.

Carstensen et al. C12,300/55: In man, STH (Somacton) has been found useful in the treatment of tuberculosis.

Guillerman et al. C15,540/55: In man, STH [source not indicated (H.S.)] allegedly exerts a very favorable effect upon tuberculosis.

Lemonde et al. C526/55: In mice, STH is beneficial in combating chronic but not acute tuberculous infection.

Lemonde C6,400/55: In mice and rats, STH has a favorable effect upon the course of experimental tuberculosis.

Brouet et al. G72,418/56: Review (47 pp., 55 refs.) on the effect of STH upon clinical and experimental tuberculosis. Personal observations on guinea pigs showed that the hormone has a moderate protective effect.

Chirico C24,381/56: Review (32 pp., about 100 refs.) on the effects of STH, with special reference to its influence upon inflammation and tuberculosis.

Wasz-Höckert & Backman C34,801/56: In guinea pigs, ACTH aggravates the course of tuberculosis. STH in itself is without conspicuous effect, however, "the strongly deteriorating effect on tuberculosis produced by ACTH was evidently counteracted by STH when given simultaneously with ACTH."

Wasz-Höckert & McCune E31,145/63: In mice infected with tuberculosis, STH caused an increase in body weight but did not inhibit the development of the infection, nor did it counteract the unfavorable effect of ACTH.

Varia ←. *Cavallero C829/54:* Review on the effect of STH, ACTH, and cortisone upon various infections, especially in the rat.

Viruses ←

Kalter et al. B49,656/50: In mice, the proliferation of influenza virus is accelerated

by STH and testosterone, presumably because of an enhanced protein synthesis in general.

Kass et al. B95,353/54: In mice, resistance to pneumococcal and influenza virus infections is depressed by pretreatment with cortisone or cortisol, but not by ACTH. STH failed to overcome the effect of cortisone and did not increase resistance to infection when given alone.

Pecori et al. C89,118/59; C89,121/59: Prednisone, triamcinolone, and dexamethasone increase the sensitivity of the mouse to infection with the MHV-3 hepatitis virus. This pro-infectious effect is largely counteracted by STH.

Cilli et al. D12,192/61: In sheep, STH, owing to its prophlogistic effect, delimits the lesions produced by variola virus. ACTH and dexamethasone exert an opposite effect.

Altucci et al. D65,819/62: In mice, STH alters the tissue reaction to infection by vaccinia virus, but has little effect upon mortality.

Parasites ←

Galliard & Lapierre E82,642/53: In mice, STH retards the development of infection with *P. berghei*.

Galliard et al. G70,892/53: In frogs, infection with *T. inopinatum* is inhibited by STH, presumably as a consequence of its phlogistic

action which favors the phagocytosis of the parasites.

Galliard et al. D89,408/54: In mice, STH greatly retards infection with *Plasmodium berghei*. STH has no effect upon either toxoplasmosis in the mouse or infection with *T. brucei* in the rat or mouse.

Fungi and Yeasts ←

Scherr C39,263/57: In mice infected with *Candida albicans*, the development of moniliasis may be either increased or decreased by cortisone, depending upon various factors, particularly the severity of the infection, sex or pregnancy. Testosterone enhanced, and STH counteracted the deleterious effect of cortisone. Gonadotrophin (pregnant mare serum) was without effect.

Bacterial Toxins ←

Jude et al. C16,220/55: In mice, STH-pre-treatment protects against subsequent infection with typhoid bacilli. The protection is ascribed to improved antibody formation and phagocytosis. STH offers no protection against typhoid endotoxin.

Skuratova D20,887/62: In mice, resistance against the fatal effect of diphtheria toxin is more markedly increased by STH than by ACTH.

Immune Reactions ←

In guinea pigs, STH has been claimed to depress tuberculin sensitivity and to synergize the desensitizing effect of cortisone.

In rats, STH aggravates the glomerular lesions characteristic of the Masugi nephritis, and increases the formation of antibodies against *Pasteurella pestis*. It also raises hemolysin formation following i.p. injection of sheep erythrocytes in the rat.

Hepatic and Renal Lesions ←

In partially hepatectomized rats, STH failed to further increase the high mitotic rate in the liver remnant.

In completely nephrectomized rats, STH slightly prolonged survival. The renal atrophy produced by temporary ligation of one renal pedicle is counteracted, and survival following removal of the contralateral kidney is prolonged by STH.

Various Stressors ←

In guinea pigs and rats, STH diminishes the catabolism, and to a lesser extent the mortality, induced by total body X-irradiation.

In the rat, STH counteracts the loss of body weight induced by chronic exposure to cold. Under certain circumstances it also prolongs survival in extreme cold, or

after severe burns. It has been claimed that in man, STH likewise counteracts the catabolism produced by burns.

STH is said to increase the EST in the rat and the salinity tolerance in the trout, and to offer "moderate protection" against various stressors in guinea pigs.

Hepatic Enzymes ←

In rats, STH decreases hepatic arginase and GPT but not GOT activity. The TPO activity of the rat liver increases with age, as well as after STH injection.

In rats, STH inhibits the synthesis of hepatic TKT and represses TKT induction by stressors or cortisol, but it has no effect upon the cortisol-induced TPO activity.

The OKT activity of the rat liver is diminished after treatment with STH, the same as after partial hepatectomy.

In rats treated with STH during the postnatal period, the development of various drug-metabolizing hepatic microsomal enzymes is suppressed.

In mice, STH first decreases and then increases hepatic TPO activity. A similar biphasic reaction is allegedly produced by exposure to stress; this may explain some of the contradictions in the published data.

Immune Reactions ←

Cornforth & Long B77,176/53: In guinea pigs sensitized to tuberculin, single s.c. injections of ATP prevent desensitization by alloxan, cortisone, and dihydro-ascorbic acid. Single s.c. injections of insulin do not in themselves influence sensitivity but prevent desensitization by alloxan and cortisone. Single s.c. injections of STH depress tuberculin sensitivity and synergize the action of cortisone or alloxan.

Dutz et al. C31,646/56: In rats, gonadectomy did not significantly change the course of Masugi nephritis, whereas a folliculoid preparation (Östravid) and testosterone ameliorated it. STH considerably aggravated the glomerular lesions and the hypertension.

Hayashida & Li C29,987/57: In rats, ACTH decreases whereas STH increases the formation of antibodies against a soluble protein envelope antigen extracted from *P. pestis*.

Ghiringhelli C90,609/60: In rabbits, the production of anti-ovalbumin antibodies is not significantly influenced by STH.

Terragna & Jannuzzi F62,290/66: Review of the literature on the influence of STH on antibody formation. Personal observations in rats show that hemolysin formation following i.p. injection of sheep erythrocytes was increased by STH, but the change was statistically not significant.

Hepatic Lesions ←

Cristensen & Jacobsen A 49,204/49: In rats subjected to partial hepatectomy, neither hypophysectomy nor thyroidectomy impairs the rate of regeneration. No significant change in mitotic rate was observed after pretreatment with stilbestrol or STH.

Selye & Bois B97,074/54: In adrenalectomized rats with choledochus ligation, cortisol enhances the accumulation of bile within the bile-duct stem and furthers the development of perforating choledochus ulcers. These actions can be prevented by concurrent treatment with STH.

Moolten et al. H 30,606/70: In rats, the rise in hepatic DNA synthesis after partial hepatectomy is accelerated by surgical interventions or STH. Cortisone, cortisol and ACTH were ineffective. Neither stress nor STH stimulated DNA synthesis significantly in non-hepatectomized rats.

Renal Lesions ←

Dési et al. C69,045/59: In rats, survival after bilateral nephrectomy is prolonged by STH and DOC, alone or in combination, but the effect of STH is diminished by concurrent administration of MAD.

Köhnlein et al. D38,961/62: In rats, the renal atrophy produced by temporary ligation

of one renal pedicle is counteracted, and survival following subsequent removal of the healthy kidney is prolonged by STH.

Various Stressors ←

Ionizing Rays ←. *Lacassagne & Tuchmann-Duplessis* E 53,832/53: In X-irradiated guinea pigs and rats, body-weight loss and to some extent even mortality, were diminished by STH.

Hoene et al. B 92,374/54: In rats, pretreatment with STH inhibits the loss of body weight and the involution of the lymph nodes following X-irradiation, but it exerts no clear-cut effect upon the involution of the spleen and thymus or the deficient antibody formation induced by irradiation.

Rigat C 10,747/55: Review (46 pp., 67 refs.) on the literature concerning the effect of hormones upon X-irradiation, with special reference to ACTH, STH, vasopressin, epinephrine, cortisone, DOC, testosterone, estradiol, progesterone, and thyroxine.

Barlow & Sellers C 21,626/55: In rats, STH prevents body-weight loss but does not prolong survival following X-irradiation.

Bloodworth et al. C 14,328/56: In rats, weight loss and mortality following X-irradiation were diminished by STH.

Temperature Variations ←. *Dugal & Dufour C* 8,603/54: In rats, the loss of body weight produced by chronic exposure to cold is counteracted by STH.

Dufour & Dugal C 15,508/55: In rats, STH increases resistance to cold.

Dufour & Dugal C 26,092/57: In rats, resistance to cold is diminished by STH or DOC given in combination with vitamin C.

Koch et. al. C 33,922/57: In rats, ACTH, unlike STH, prolongs survival following severe burns.

Soroff et al. G 52,127/67: In man, human STH counteracts the catabolism produced by burns.

Varia ←. *Rosenblum C* 5,974/55: In rats "ACTH and cortisone acetate in combination with vasopressin each produced a greater fall in EST than was produced by vasopressin alone. In contrast, STH in combination with vasopressin prevented the fall induced by vasopressin alone and produced its usual elevation in the EST."

Smith C 46,496/56: In brown trout, thyroxine raises, whereas thiourea and thiouracil

reduce salinity tolerance. Anterior pituitary extracts and STH likewise raise salinity tolerance, whereas posterior lobe extracts, testosterone, gonadotrophin, TTH, and ACTH have no such effect.

Amante C 62,537/58: In guinea pigs, STH "moderately protects" against the stress of burns, tourniquet, or evisceration.

Vanamee et al. H 32,254/70: In rats, the production of stress ulcers of the stomach by restraint is inhibited by pretreatment with STH.

Hepatic Enzymes ←

Beaton et al. B 86,367/53: In adult male rats, a single i.p. injection of STH causes a decrease in the rate of urea formation by liver slices, as well as in the hepatic arginase and GPT but not GOT activity. No such changes were noted in young male rats.

Wood Jr. & Knox D 81,779/54: In mice, STH decreases hepatic TPO activity.

Beaton et al. C 10,012/55: STH decreases the hepatic GPT and d-aminoacid oxidase activity in nonpregnant female rats. These effects are even more pronounced if the animals receive STH + "equine estrogenic substances" + progesterone. This enzyme activity also decreases during pregnancy both in intact and in hypophysectomized rats.

Wood et al. C 27,721/56: In mice bearing SC-sarcoma implants, the hepatic TPO activity was first diminished, but rose above normal as the neoplasms grew. "Changes analogous to this biphasic depression and elevation of the enzyme level in tumor-bearing animals could be produced in control mice by growth hormone and by adrenal-stimulating stress, respectively."

Beaton et al. D 83,636/57: Following STH treatment, there is a significant depression in the GPT activity of rat liver tissue, whereas cortisone has an inverse effect.

Zuchlewski & Gaebler D 91,862/57: Hepatic glutamic acid dehydrogenase activity increases after hypophysectomy in the rat, and it is not altered by STH in either hypophysectomized or sham-operated control animals. GPT and GOT activities have also been investigated under similar conditions.

Rosen et al. C 50,741/58; *C* 71,414/59: Marked increases in GPT activity were observed in the livers of rats given cortisol, cortisone, 9 α -fluorocortisol, prednisone, 6 α -methylprednisolone, 9 α -fluoro-21-desoxy-6 α -methylprednisolone or ACTH, whereas two nonglucocorticoid cortisol derivatives, 11-epi-

cortisol and 9 α -methoxycortisol were inactive. STH, testosterone, and insulin caused no significant change in GPT by themselves, nor did they modify the action of cortisol. On the other hand, large doses of estradiol and thyroxine caused a moderate increase in GPT activity but when injected simultaneously with cortisol, they appeared to interfere with its action as did progesterone. Adrenalectomy slightly diminished or failed to affect the GPT inducing activity of cortisol, whereas hypophysectomy caused a rise in GPT activity and augmented the effect of cortisol.

Rivlin & Knox C71,249/59: The TPO activity of rat liver increases with age and body weight, as well as after STH injection.

Kenney & Albritton G64,557/65: Review of the literature suggesting that transaminase induction in response to stressors can be due to corticoid secretion during the stress reaction. Cortisol enhances enzyme synthesis after an increased rate of synthesis of ribosomal transfer and "DNA-like" RNA's. The present experiments confirm the view that repressor(s) can inhibit enzyme synthesis at the translational level because inhibition of RNA synthesis can prolong the corticoid-induced increase in enzyme synthesis under suitable conditions. "Administration of stressing agents (tyrosine, Celite) to adrenalectomized rats initiates a highly selective repression of the synthesis of hepatic TKT. The enzyme level falls with a $t_{1/2}$ of about 2.5 hr. Immunological measurement of the rate of enzyme synthesis indicates that it is reduced essentially to zero in stressed, adrenalectomized rats, whereas labeling of total liver soluble proteins is unaffected. Actinomycin does not itself influence the enzyme level, but it blocks the stress-initiated repression of enzyme synthesis, indicating that repression acts at the translational level, whereas initiation of repression involves transcriptional processes." In hypophysectomized rats, stressors are ineffective, and preliminary data suggest that STH is responsible for transaminase repression.

Rinaudo et al. F95,471/67: Studies on the induction of various hepatic enzymes by STH and LTH in toad tadpoles.

Kenney G50,810/67: In intact, hypophysectomized or adrenalectomized rats, STH inhibits the synthesis of hepatic TKT. The rate of enzyme synthesis is reduced nearly to zero (immunochemical-isotopic analyses), whereas labeling of the bulk of the liver proteins is increased by STH. Repression is blocked when RNA synthesis is inhibited by actino-

mycin-D. STH also appears to play a role in the repression of TKT induction by stressors. A hypophysectomized and an intact rat were united by parabiosis. When the pituitary-bearing member was stressed by tyrosine i.p., repression occurred in the livers of both treated and untreated (hypophysectomized) animals. Transaminase levels were unchanged in one single experiment, where the stressing agent was administered to the hypophysectomized partner.

Räihä & Kekomäki G68,114/68: In the rat, the OKT activity of the liver is very low in the fetus; it exhibits a small transient elevation around term, then drops, and eventually reaches the high adult activity level during the third postnatal week. Triamcinolone given postnatally causes a pronounced elevation of OKT, but has no such effect in fetal or adult rats. Puromycin prevents the rise in OKT after triamcinolone administration. In adult rats fed a protein- or arginine-free diet, OKT activity decreases and fails to rise under the influence of triamcinolone. Partial hepatectomy or STH depresses OKT-activity in the livers of adult rats.

Schapiro H2,360/68: Stress (30 min rough agitation in a noisy laboratory shaker) had no effect upon the corticoid sensitive enzyme TKT in the liver of the intact rat, but it increased TPO activity, which is likewise corticoid inducible. Adrenalectomized rats, similarly stressed, exhibited a decreased transaminase activity with no change in TPO. This inhibitory effect was abolished by hypophysectomy. STH inhibited induction of transaminase by cortisol, but had no effect upon cortisol-induced TPO activity. The opposing actions of STH and glucocorticoids may be involved in adaptive reactions to stress.

Schapiro et al. H12,411/69: Brief abstract stating (without giving experimental details) that "the severe stress of laparotomy in the intact adult rat induces a large corticoid-dependent increase in transaminase activity. STH administered simultaneously, or one hour before laparotomy will completely inhibit this enzyme increase. During the early postnatal period, however, STH will not block transaminase induction caused by cortisol or laparotomy."

Wilson G69,098/69: In the rat, in vitro studies suggest that STH depresses hexobarbital, aminopyrine and ethylmorphine metabolism. ACTH and LTH have no such effect and

do not influence the corresponding action of STH. [The hormones were administered s.c. 48 hrs before removal of the liver for the metabolic studies (H.S.).]

Wilson H 21,345/70: In rats, the development of various drug-metabolizing hepatic microsomal enzymes can be suppressed by postnatal treatment with STH.

**← OTHER ANTERIOR PITUITARY PREPARATIONS
(LTH, GTH, TTH, CRUDE EXTRACTS)**

Many of the experiments concerning the protective action of LTH, GTH, TTH and other anterior pituitary extracts, were performed with more or less purified preparations in which several hormones were present; hence, we shall discuss these experiments conjointly. Most of the relevant work is concerned with the effect of anterior pituitary extract upon resistance to drugs, infections, hypoxia, and various forms of nonspecific stress.

Drugs ←

Resistance of mice to acetonitrile is considerably increased by thyroid preparations, and hence, it is not surprising that the thyrotrophic hormone (TTH) has a similar effect. However, gonadotrophic urinary extracts and folliculoid preparations also increase acetonitrile resistance in the mouse; hence, this phenomenon is not truly characteristic for the thyroid hormones.

Pretreatment of rats with crude lyophilized anterior pituitary preparations makes them particularly sensitive to the anesthetic effect of pentobarbital and progesterone. However, this effect is also nonspecific, since various tissue extracts and proteins, such as egg white, casein, etc., prolong pentobarbital anesthesia.

The hepatotoxic effect of CCl_4 is partially prevented by crude anterior pituitary extracts in the rat.

Among the carcinogens, AAF is especially active in producing neoplastic lesions in the rat liver. This effect is intensified by pregnant mare serum, gonadotrophin, but also by estradiol and testosterone. The detoxication of N-OH-AAF is inhibited in rats bearing functional pituitary-tumor transplants, which also enhance hepatic carcinogenesis.

In rabbits, cholesterol atheromatosis is aggravated by TTH. According to some investigators, the severity of the lesions roughly parallels the blood cholesterol level, whereas others claim that TTH decreases the hypercholesterolemia. In cockerels, neither chorionic gonadotrophin nor TTH has any clear-cut effect upon cholesterol atherosclerosis.

In rats, the production of cardiac lesions by emetine, as well as of vascular changes by ergotamine, are inhibited by various gonadotrophic preparations.

The action of lathyrogens upon the bones of the rat is aggravated by luteotropic hormone (LTH) as well as by STH.

On the other hand, the osteoclastic bone absorption produced by vitamin-A overdosage in rats, though prevented by STH, is not influenced by LTH.

***Microorganisms and Their Products* ←**

Various anterior pituitary preparations are said to protect mice against bacterial infection, (e.g., with *B. anthracis*, *E. coli* and *Ps. pyocyaneus*), but not against several other organisms.

In rabbits, the progress of tuberculosis is accelerated by LH. In mice, the tuberculosis is not significantly affected by TTH, nor is infection with *Candida albicans* demonstrably altered by gonadotrophin.

Various gonadotrophic preparations have been claimed to counteract the lethal effects of diphtheria toxin in guinea pigs.

Hypoxia ←

In rats and guinea pigs, pretreatment with crude anterior pituitary extracts diminishes resistance to decreased oxygen pressure, presumably as a consequence of their TTH content, since thyroidectomy abolishes this effect. Resistance to hypoxia is also decreased in guinea pigs by purified TTH, an observation which is in agreement with the well-known fact that thyroid hormones act in this manner.

Hormones ←

Masson et al. B48,694/49: In rats sensitized by uninephrectomy + NaCl, DOC produced more severe hypertension than a crude anterior pituitary powder (APP). Combined treatment with DOC + APP had no additive effect.

Oester C84,324/59: The calcifying arteriosclerosis produced by repeated i.v. injections of epinephrine in the rabbit is aggravated by thyroxine and T3 s.c., but not by TTH or dinitrophenol. Thyroidectomy, unlike propylthiouracil, inhibits the epinephrine arteropathy.

Blatt et al. H19,832/69: In frog tadpoles, prolactin antagonizes thyroxine-induced tail regression in the course of metamorphosis, but pancreatic regression and acid phosphatase development in the liver are not inhibited. Thus, prolactin does not antagonize the entire process of metamorphosis some events of which may not be directly induced by thyroxine.

Drugs ←

Acetonitrile ←. *Eufinger et al. 22,082/29:* In mice, acetonitrile resistance is increased by pretreatment with human pregnancy serum. It remains to be seen whether this is due to an increased serum level of GTH, TTH or of other metabolites.

Eufinger & Wiesbader 4,663/30: In mice, pretreatment with gonadotrophic urinary extracts or folliculoid preparations increases acetonitrile resistance and hence this phenomenon is not characteristic for thyroid hormones.

Neuweiler 43,582/32: In mice, it was not possible to increase acetonitrile resistance by a

variety of gonadotrophic hormone preparations, including the serum of pregnant women.

Sommer 44,648/34: In mice, acetonitrile resistance is increased by a variety of gonadotrophic preparations, including the serum of pregnant women.

Fellinger & Hochstädt 63,744/35: In mice, the protection against acetonitrile offered by thyroxine or TTH is blocked by an extract of blood which contains the "ether soluble anti-thyroid substances."

Wiesbader 68,823/36: In mice, acetonitrile resistance is increased not only by thyroid extract but also by TTH and various gonadotrophic preparations.

Actinomycin ←. *Tuchmann-Duplessis & Mercier-Parot H28,876/70:* In rats, LTH does not prevent the abortifacient and teratogenic actions of actinomycin.

Anaphylactoid Edema ←. *Higginbotham & Dougherty C44,529/57:* In mice, ACTH increased the toxicity of polymyxin B; STH and TTH had no effect upon it.

Barbiturates ←. *Selye & Masson A97,571/44:* Pretreatment of rats with lyophilized anterior pituitary (LAP) makes them particularly sensitive to the anesthetic effect of progesterone or pentobarbital.

Masson B275/45: Male rats are more resistant to pentobarbital anesthesia than females. However, upon treatment with LAP s.c., resistance decreased considerably in both sexes, and eventually reached the same low level in males and females. LAP produced a similar increase in sensitivity to amobarbital, hexobarbital, cyclobarbital and inbarbital, but did not influence barbital or phenobarbital anesthesia.

Masson A95,888/46: In rats, not only anterior pituitary preparations, but extracts of

various tissues, as well as egg white, casein, and other proteins prolonged pentobarbital anesthesia. Presumably, "the assimilation of foreign proteins interferes with some important mechanism necessary for the detoxification of barbiturates."

Masson B1,217/46: In male rats, pretreatment for 6 days with crude pituitary powder s.c. "slightly prolonged the duration of anesthesia with phanodorn, thiethamyl, neonal, delvinal, nystal and amyral, and greatly prolonged (2 to 5 times) with pentothal, seconal, allyl pental, nembutal, evipal, pernoston and sigmodal." There was no difference between the pretreated and control rats as regards the anesthetic effect of phenobarbital, probarbital, barbital, aprobarbital, diallyl barbituric acid and trichloroacetaldehyde. "The action of pituitary preparations is not specific but can also be obtained with preparations from various organs and with foreign proteins." Hepatic damage is considered to be a likely cause of the prolongation of anesthesia under these conditions.

Cadmium ←. *Pařízek et al. H7,672/68:* In adult rats in which persistent estrus had been induced by a single s.c. injection of testosterone or 19-nortestosterone on the fifth day of life, cadmium s.c. elicited particularly severe ovarian changes. Pretreatment with pregnant mare serum gonadotrophin protected the ovaries of such animals.

Carbon Tetrachloride ←. *Masson 96,335/47:* The hepatotoxic action of CCl_4 is aggravated by DOC and testosterone but partially prevented by anterior-pituitary extracts in the rat.

Arrigo & Trasino C21,687/55: In rats, crude alkaline anterior-pituitary extracts (rich in STH) do, whereas acid extracts (rich in ACTH and STH) do not protect the liver and pancreas against damage by CCl_4 . Cortisone protects the liver but not the pancreas.

Julius 29,127/34: In mice, the production of skin cancers by topical application of tar was not prevented by a gonadotropic extract of pregnancy urine.

Carcinogens ←. *Cantarow et al. B18,774/46:* In rats given AAF p.o., the development of cystic and neoplastic hepatic lesions was accelerated and intensified by GTH (pregnant mare serum), estradiol, and testosterone, but inhibited by thiouracil. "This phenomenon may be related on the role of the liver in the intermediary metabolism and excretion of the sex steroid." In the hyperplastic target organs of the sex hormones tumors did not occur, in

contrast to the high incidence of tumors in the thyroids of rats given thiouracil simultaneously with the carcinogens.

Stasney et al. B26,653/47: In rats, 2-acetaminofluorene feeding produces mammary carcinoma only in females, and its development is not significantly accelerated by estradiol or gonadotrophin. "Malignant lesions of the liver occurred in 54.8 per cent of females and 92.3 per cent of males receiving the carcinogen alone. Administration of estradiol and PMS gonadotrophin to females and of testosterone and chorionic gonadotrophin to males intensified the cystic and neoplastic hepatic lesions induced by 2-acetaminofluorene."

Weisburger et al. D18,583/64: In rats fed a diet containing N-hydroxy-N-2-fluorenylacetamide, implantation of Furth's mammatropic tumor MtT/F4, as a source of pituitary hormones, accelerated hepatic carcinogenesis.

Shirasu et al. F65,704/66: In rats, the detoxication of N-hydroxy-N-2-fluorenylacetamide (N-OH-FAA) is inhibited by the transplantation of functional pituitary tumors which may account for their enhancing effect upon hepatic carcinogenesis.

Cholesterol ←. *Bruger & Fitz A15,324/38:* In cholesterol-fed rabbits, atheromatosis of the aorta is aggravated by chronic treatment with TTH. The severity of the lesions roughly parallels the blood cholesterol level.

Turner & De Lamater A37,602/42: In cholesterol-fed rabbits, TTH markedly reduces hypercholesterolemia even after thyroidectomy. [Vascular changes are not described (H.S.).]

Stamler et al. B91,353/53: In cholesterol-fed chicks, coronary atherosclerosis is prevented by estradiol even if the feminizing effects are eliminated by concurrent administration of testosterone. The protective effect of the folliculoid is not due to its effect upon blood cholesterol, since hypercholesterolemia remains uninfluenced by it, but estradiol elevates the plasma phospholipid levels. In itself, neither testosterone nor chorionic gonadotrophin affects coronary atherosclerosis under these conditions.

Stamler et al. C81,655/58: TTH—unlike thyroid preparations—failed to influence cholesterol atherosclerosis in cockerels.

Emetine ←. *de Gregorio & Armellini G64,277/64:* In rabbits, the production of cardiac lesions by emetine is inhibited by chorionic gonadotrophin and testosterone but not by estradiol.

Scafidi & Arrigo G62,941/68: In rabbits, the cardiac lesions produced by emetine are

inhibited by various gonadotrophic hormone preparations.

Ergotamine ←. *Bolis E50,716/56:* In rats, various gonadotrophic preparations diminish the organ lesions produced by toxic doses of ergotamine.

Messina G18,016/64: In rats, ergotamine produces vascular lesions conducive to tail necrosis more readily in females than in males. Hypophysectomy prevents these toxic manifestations in both sexes, whereas treatment with chorionic gonadotrophin does not affect them.

Ethionine ←. *Farber & Segaloff D95,996/55:* In ovariectomized rats, various testoids and STH protected the liver against fatty infiltration produced by ethionine i.p., whereas cortisone and ACTH aggravated it. Estradiol, DOC, and TTH had no effect.

Glycine ←. *Hay 93,491/47:* In rats, the hepatotoxic and nephrotoxic actions of glycine-enriched diets are not significantly modified by crude anterior pituitary extracts.

Lathyrogens ←. *Selye C31,369/57:* In the rat, the osteolathyrism produced by AAN is aggravated by STH, LTH, and partial hepatectomy, but it is inhibited by ACTH, cortisol, or estradiol.

Morphine ←. *Benetato et al. 33,773/35:* In rats, neither adrenocortical extract nor an adrenotropic anterior pituitary preparation altered resistance to morphine or to typhoid-parathyroid vaccine.

p-Nitrobenzoic Acid ←. *Wilson G63,125/68:* In young rats, transplants of a pituitary mammatropic tumor "did not prevent an increase in the liver microsomal metabolism of hexobarbital or the formation of formaldehyde from aminopyrine which followed phenobarbital pretreatment. High levels of somatotropin, corticotropin, and prolactin in blood, or possibly some other unknown factors produced by this tumor, appeared to prevent the normal development of the liver enzyme system which metabolized hexobarbital, aminopyrine, and p-nitrobenzoic acid in the rat."

Reserpine ←. *Wirtheimer D10,158/59:* In rats, the production of gastric ulcers by reserpine is enhanced following pretreatment with various impure gonadotrophic hormone preparations.

Vitamin A ←. *Schneider & Widmann 33,725/35:* In guinea pigs, both thyroidectomy and treatment with TTH considerably alter vitamin-A metabolism.

Mayer & Goddard B55,008/51: In rats deficient in vitamin A, the atrophy of the accessory sex organs is abolished by chorionic gonadotrophin, suggesting that the defect is not due to an inability of the gonads to secrete testoids but to inadequate pituitary gonadotrophin secretion.

Selye C36,050/57: In rats, the intense osteoclastic bone absorption produced by vitamin-A overdosage can be prevented by STH. Although the luteotropic hormone (LTH) shares many of the actions of STH, it cannot substitute for the latter in counteracting vitamin-A intoxication.

Vitamin C ←. *Agnoli 2,633/32:* In guinea pigs, neither crude pituitary extracts nor urinary gonadotrophins ameliorate the course of scurvy on vitamin-C deficient diets.

Varia ←. *Störtebecker 76,398/39:* Review of the early literature (1913—1937) on the effect of the pituitary upon drug resistance.

Microorganisms and Their Products ←

Bacteria ←. *Weinstein B15,029/39:* In mice, various anterior pituitary preparations protect against infection with *B. anthracis*. Parathyroid extract was also very effective, whereas thyroxine and testosterone offered little protection while progesterone, insulin, "estrin" and posterior lobe extract were virtually ineffective.

Weinstein A33,940/40: In mice, neither parathyroid extract nor a crude anterior pituitary preparation offered protection against infection with *Klebsiella pneumoniae*, but they did improve survival after inoculation of *E. coli* or *Ps. pyocyaneus*.

Lurie et al. B31,933/49: In rabbits, estradiol retards the progress of experimental tuberculosis at the portal of entry in the skin and diminishes its dissemination to internal organs, presumably by reducing the permeability of connective tissue. Chorionic gonadotrophin has an inverse effect.

Lurie et al. B31,931/49; B31,932/49: In highly inbred, sexually mature rabbits, estradiol retarded the progress of tuberculosis following i.c. inoculation. In immature rabbits, estradiol was less effective. LH accelerated the progress of the disease, whereas ovariectomy or progesterone remained without effect.

Schäfer B99,955/54: Monograph (127 pp., numerous refs.) on the role of endocrine factors in tuberculosis. Special sections are devoted to

the hormones of the thyroid, parathyroid, thymus, adrenals, pancreas, and gonads.

Youmans & Youmans B95,169/54: In mice, cortisone markedly reduced the survival time after infection with human tubercle bacilli, and this effect could not be prevented by STH. Given alone, ACTH, STH, and TTH likewise failed to influence the course of the infection.

Meier & Neipp C37,215/56: In mice, the chemotherapeutic action of sulfonamides against resistant Type III pneumococci is increased by various gonadotrophic and STH preparations. However, certain bacterial polysaccharide fractions possess a similar effect, and hence, the latter is presumably not dependent upon the specific actions of the hormone preparations.

Scherr C39,263/57: In mice infected with *Candida albicans*, the development of moniliasis may be either increased or decreased by cortisone, depending upon various factors, particularly the severity of the infection, sex or pregnancy. Testosterone enhanced, and STH counteracted the deleterious effect of cortisone. Gonadotrophin (pregnant mare serum) was without effect.

Bacterial Toxins ←. *Ciulla & Razzini B50,987/39:* In guinea pigs, pretreatment with pregnancy urine gonadotrophins diminishes the lethal effect of diphtheria toxin.

Tonutti B48,892/50: In guinea pigs, diphtheria toxin produces marked hemorrhagic necrosis of the testes and ovaries only after pretreatment with gonadotrophic hormones.

Scaffidi & Fidecaro G51,129/65; G43,543/66: In guinea pigs, the cardiopathy produced by diphtheria toxin can be prevented by chorionic gonadotrophin and cocarboxylase.

Hypoxia ←

Houssay & Rietti 3,187/32; 3,283/32: In rats pretreatment with an impure pituitary extract diminishes resistance against hypoxia, but this effect is abolished by thyroidectomy, and is presumably due to TTH. In untreated rats, thyroidectomy actually increases resistance to anoxia.

Houssay & Rietti 5,793/32: In guinea pigs, resistance to decreased oxygen pressure is diminished by anterior pituitary extract, presumably through its TTH content since the effect is abolished after thyroidectomy.

Rotter A63,564/42: In guinea pigs, altitude tolerance is greatly reduced by pretreatment with TTH.

Varia ←

Henriques et al. B24,140/48: In rats sensitized by uninephrectomy, the production of hyalinosis and hypertension by crude anterior pituitary extracts is facilitated if the diet is rich either in protein or in amino-acids.

Smith C46,496/56: In brown trout, thyroxine raises, whereas thiourea and thiouracil reduce salinity tolerance. Anterior pituitary extracts and STH likewise raise salinity tolerance, whereas posterior lobe extracts, testosterone, gonadotrophin, TTH, and ACTH have no effect.

Osipovich C58,570/57: In uninephrectomized rats, methylthiouracil enhances compensatory hypertrophy of the remaining kidney, presumably as a consequence of increased TTH secretion. The acceleration of compensatory renal hypertrophy by exposure to cold is ascribed to a similar mechanism.

Glenn et al. G70,204/60: Review (48 pp., 11 refs.) on the effect of various steroids, ACTH, GTH, ovariectomy and adrenalectomy upon the development of C3H mammary carcinoma transplants in mice and fibroadenomas in rats.

Knigge C97,819/60: Review on the neuroendocrine mechanisms influencing ACTH and TTH secretion particularly during adaptation to cold.

Bucher G68,621/63: Review on the influence of hypophysectomy and hypophysial hormones upon hepatic regeneration.

Fisher & Fisher F74,176/66: In rats, the incidence of metastases from Walker tumor transplants is not significantly altered by thyroidectomy, propylthiouracil, thyroxine or TTH.

Preisig et al. F70,515/66: In acromegalic patients, biliary BSP excretion is increased. [It is not known which, if any, of the hormones secreted by the hyperactive pituitary are responsible for this effect (H.S.).]

Rinaudo et al. F95,471/67: Studies on the induction of various hepatic enzymes by STH and LTH in toad tadpoles.

Sakamoto & Prasad F95,441/67: In mice and rats, β -MSH offers moderate protection against X-irradiation under certain conditions.

← POSTERIOR PITUITARY PREPARATIONS

In dogs and guinea pigs, vasopressor pituitary extracts offer partial protection against histamine intoxication. In rats, the production of renal cortical necrosis by vasopressin is greatly facilitated by 5-HT and folliculoids.

It has been claimed that vasopressor posterior pituitary extracts influence the toxicity of various drugs through different mechanisms. They may improve resistance to hypotensive drugs because of their vasopressor effect, or aggravate the toxicity of substances normally eliminated through the kidney, because of their antidiuretic action. However, none of these effects was shown to be sufficiently striking to have deserved extensive investigation, except for the well-known aggravation of water intoxication by vasopressin.

Under certain circumstances, vasopressin has also been claimed to offer protection against various infections, X-irradiation, hemorrhage, anoxia, electroshock and traumatic shock. On the other hand, vasopressin aggravates or fails to influence the damaging effect of various bacterial toxins, hyperoxygenation, and exposure to cold.

Steroids ← cf. Selye C 50,810/58, pp. 83, 84; C 92,918/61, p. 124; G 60,083/70, p. 334.

Hormones and Hormone-Like Substances ←

Best & Solandt A 33,635/40: In dogs, shock produced by histamine, trauma, or hemorrhage is successfully treated by vasopressor pituitary extracts.

Kowalewski & Bain C 3,897/54: In guinea pigs, a vasopressor posterior pituitary extract given s.c., 10 min before the injection of histamine, prevented the induction of gastric ulcers, presumably because of an antagonistic interaction at the level of the vascular system.

Drugs ←

Acetonitrile ←. **Paal** 22,603/30: In mice, acetonitrile resistance is not consistently influenced by posterior pituitary extract (hypophysin), a folliculoid preparation (progynon), or epinephrine.

Barbiturates ←. **Werle & Lentzen** A 28,007/38: In dogs and rabbits, various vasoactive substances (epinephrine, histamine, vasopressin, kallikrein) tend to prolong the anesthetic effect of pronarcon and hexobarbital.

Rümke G 69,768/63: In mice, small doses of vasopressin i.v. failed to prolong hexobarbital sleeping time.

Hexobarbital ← Vasopressin, Gp, Mouse: Lamson et al. C 14,547/51*; Rümke G 69,768/63*

Pentobarbital ← Vasopressin + H₂O, Mouse: Borzelleca et al. C 40,953/57*

Bromoethylamine Hydrobromide ←. **Fuwa & Waugh** F 96,546/68: In rats, the renal papillary necrosis produced by bromoethylamine hydrobromide is inhibited by vasopressin, presumably as a consequence of its antidiuretic effect.

Carcinolytic Agents ←. **Connors et al.** G 17,080/64: In rats, Mannitol Myleran is normally excreted unchanged in the urine within 5 hrs after i.p. administration. Pretreatment with antidiuretic hormone potentiates both its lethal and antitumor action, presumably because it diminishes excretions.

Chlorpromazine ←. **Khrabrova** D 49,985/61: In cats, electroshock is effectively antagonized by chlorpromazine if the hypotensive action of the latter is prevented by vasopressin.

Chloral Hydrate ←. **Fastier et al.** C 37,038/57: In mice, chloral hydrate sleeping time is increased by epinephrine, norepinephrine, phenylephrine, methoxamine, 5-HT, histamine, ergotamine, yohimbine and atropine. "It is suggested that some, at least, of the drugs which prolong the effects of hypnotics do so by virtue of a hypothermic action." Vasopressin, cortisone, and DOC did not prolong chloral hydrate sleeping time at the doses tested.

Cholesterol ← cf. also Selye G 60,083/70, p. 335. **Cooper & Gutstein** F 61,290/66: In rabbits, calcific aortic atherosclerosis is produced by combined treatment with cholesterol and vasopressin.

Digitalis ←. *Ghedini & Ollino A 21,128/14:* Brief mention of observations on rabbits showing that pretreatment with Pituitrin modifies the hemodynamic actions of digitalis "unfavorably" and those of strophanthin "favorably." [For lack of details, these findings cannot be evaluated (H.S.).]

Nash et al. G9,641/64: In rats, the toxic cardiac effects of ouabain are antagonized by synthetic oxytocin and by reserpine.

Ethanol ←. *Baïsset & Montastruc D 34,473/62; D 37,918/62:* In dogs, the development of a polyuria and polydipsia, following administration of ethanol, as well as the gradual development of a craving for alcohol are prevented by vasopressor posterior lobe extract.

Morphine ←. *Gruber et al. 2,199/31:* In dogs, a vasopressor pituitary extract temporarily lowers the increased general tonus of the intestine produced by morphine.

Adler et al. G79,852/57: In Sprague-Dawley rats, given ^{14}C -labeled morphine, the ratio of bound to free morphine is 2–3 times greater in the urine and plasma than in Long-Evans rats. The tissues of adrenalectomized rats of both strains contain higher concentrations of ^{14}C -labeled morphine than do control rats. Plasma bound morphine levels indicate no impairment of morphine conjugation. Vasopressin increases, whereas ACTH decreases morphine sensitivity. Yet both after ACTH and after vasopressin, tissue concentrations of morphine are either reduced or unaffected in marked contrast to the increased values after adrenalectomy. Apparently, the decreased morphine sensitivity induced by ACTH is not reflected by lower brain morphine concentrations.

Paraphenylendiamine ←. *Meissner E 52,567/19:* The head and neck edema produced by paraphenylendiamine in the rabbit is not prevented by epinephrine, posterior pituitary extract or thyroid extract.

Pentylenetetrazol ←. *Boeri C 78,610/58:* In guinea pigs, cortisone, ACTH, and vasopressin aggravate pentylenetetrazol convulsions.

Phosgene ←. *Rothlin B 30,696/47:* In rats, phosgene (COCl_2) intoxication is effectively combated by posterior pituitary extract as well as by ergotamine, presumably as a consequence of their vasoconstrictor effect.

Potassium ← cf. *Selye C 92,918/61, pp. 83, 124, 188.*

Sodium Chloride ←. *Baïsset et al. C 55,475/57:* In the rat and dog, posterior pituitary extracts favorably influence the manifesta-

tions of chronic NaCl-overdosage and prolong survival.

Baïsset et al. C 84,788/58: In rats and dogs, the effects of NaCl-overdosage are ameliorated by posterior pituitary extracts and aggravated by NaCl.

Suxamethonium ←. *Keil D 27,254/62:* In rabbits, sheep and pigs, oxytocin did not modify resistance to suxamethonium.

Strychnine ←. *Marañón & Aznar 46,926/11:* In frogs, the fatal convulsions produced by strychnine can be prevented if, prior to injection, the drug is mixed with extracts of the posterior pituitary, the thyroid, various other tissues, and particularly epinephrine. [The possibility of delayed absorption owing to local vasoconstriction has not been considered (H.S.).]

Vitamin D ← cf. *Selye C 92,918/61, pp. 124, 188; G 60,083/70, pp. 335, 336.*

Vitamin E ←. *Houchin & Smith B 6,967/44:* Rabbits deprived of vitamin E, show increased sensitivity to posterior pituitary extracts.

Water ←. *Liling & Gaunt 89,147/45:* In rats, vasopressin aggravates the manifestations of water intoxication, even if the animals are adapted by previous administration of water loads.

Waltregny & Mesdjian F 85,818/67: In cats, combined treatment with "posterior lobe extract" s.c. and large amounts of distilled water i.p. produces a condition of epilepsy with a characteristic EEG as a consequence of water intoxication.

Bacteria ← cf. also *Selye G 60,083/70, p. 335.*

Lauber 9,102/32: Observations on the effect of vasopressin, epinephrine, thyroid extract and insulin upon streptococcal and staphylococcal infections in mice.

Weinstein B 15,029/39: In mice, various anterior pituitary preparations protect against infection with *B. anthracis*. Parathyroid extract was also very effective, whereas thyroxine and testosterone offered little protection, while progesterone, insulin, "estrin" and posterior lobe extract were virtually ineffective.

Bacterial Toxins ← cf. also *Selye G 60,083/70, p. 335.*

Bailey A 1,154/17: In rabbits, vasopressin aggravates the vascular lesions produced by diphtheria toxin.

Altura et al. F 43,209/65: In rats, norepinephrine and angiotensin fail to prolong survival after traumatic shock, temporary ligation of the superior mesenteric artery, or

endotoxin shock. However, vasopressin (PLV-2) was significantly effective in traumatic and intestinal ischemia shock, but not in endotoxinemia.

Ionizing Rays ←

Gray et al. B68,316/52: In rats, pretreatment with either epinephrine or vasopressin diminishes mortality after total body X-irradiation.

Gray et al. B69,100/52: In rats, pretreatment with vasopressin or epinephrine increases survival following exposure to lethal X-irradiation.

Hervé D78,167/54: In mice, an oxytocic posterior lobe preparation increases resistance against total body X-irradiation.

Rigat C10,747/55: Review (46 pp., 67 refs.) on the literature concerning the effect of hormones upon X-irradiation, with special reference to ACTH, STH, vasopressin, epinephrine, cortisone, DOC, testosterone, estradiol, progesterone, and thyroxine.

Bacq & Beaumariage C87,128/60: In mice, synthetic oxytocin (Syntocinon) increases resistance to total body X-irradiation.

Hemorrhage ←

Best & Solandt A33,635/40: In dogs, shock produced by histamine, trauma, or hemorrhage is successfully treated by vasopressor pituitary extracts.

Cort et al. F23,086/64: In dogs, various synthetic extended-chain analogues of vasopressin and oxytocin exert a beneficial effect upon hemorrhagic shock.

Cort et al. F96,105/68: In dogs, certain vasopressin analogues offer protection against hemorrhagic shock.

Hypoxia and Hyperoxygénéation ←

Campbell A14,903/37: In rats exposed to six atmospheres of oxygen in a pressure chamber, subsequent decompression is better tolerated at low than at high external tempera-

tures. "Using an external temperature of 24°C and white rats of about 80 g, the following substances, administered subcutaneously, are found to enhance oxygen poisoning: thyroxin (0.4 mg), dinitrophenol (1.5 mg), ac-tetrahydro- β -naphthylamine (0.5 c.c., 1 p.c.), adrenaline (0.02 mg), pituitary extract (posterior lobe, above 3.5 units), insulin (0.025 u.) and eserine (0.045 mg administered with atropine 0.075 mg). These doses in themselves are harmless."

Parkes B63,024/51: In mice, resistance to anoxia is increased by posterior lobe extract as well as by ACTH preparations containing posterior lobe principles.

Electric Stimuli ←

Rosenblum C5,974/55: In rats, "ACTH and cortisone acetate in combination with vasopressin each produced a greater fall in EST than was produced by vasopressin alone. In contrast, STH in combination with vasopressin prevented the fall induced by vasopressin alone and produced its usual elevation in the EST."

Khrabrova D49,985/61: In cats, electroshock is effectively antagonized by chlorpromazine if the hypotensive action of the latter is prevented by vasopressin.

Varia ←

Best & Solandt A33,635/40: In dogs, shock produced by histamine, trauma or hemorrhage is successfully treated by vasopressor pituitary extracts.

Marino et al. D58,761/63: In guinea pigs, the cardiopathy produced by vasopressin intoxication is aggravated by concurrent exposure to a psychologic stress situation (preconditioning followed by conflict situation).

Zilberstein C80,282/60: In rats, 5-HT, vasopressin and reserpine lower resistance to cold allegedly because they interfere with pituitary hormone secretion and cause a state of "temporary functional adrenalectomy."

← HYPOPHYSECTOMY AND HYPOTHALAMIC LESIONS

The effects of adrenalectomy, orchidectomy and ovariectomy are discussed with the steroids, since ablation of these glands acts upon resistance mainly by creating a lack of steroid hormones. On the other hand, hypophysectomy will be discussed here (immediately following the pituitary hormones) together with hypothalamic lesions, since both of these operations act upon resistance primarily through their

effect upon pituitary hormone secretion. Yet, it must be remembered that, secondarily, several hypophyseal principles (e.g., ACTH and the gonadotrophins) do influence susceptibility to damaging agents through their regulating effect upon steroid secretion.

Steroids ←

It has long been noted that the hyalinosis, polyuria and hypertension produced by mineralocorticoids in rats (conditioned by uninephrectomy + NaCl) are prevented, or at least greatly diminished by hypophysectomy. STH, ACTH and TTH all play important roles in the pathogenesis of this syndrome (as do various steroids and thyroid hormones secreted under pituitary control); hence, it is not clear to what extent the prophylactic effect of hypophysectomy is due to the lack of one or the other hypophyseal hormone.

Phenobarbital increases the estradiol-metabolizing activity of hepatic microsomal enzymes in immature female rats. It also diminishes the uterotrophic effect of this folliculoid. Neither hypophysectomy nor adrenalectomy prevents this phenobarbital-induced estradiol resistance, indicating that the barbiturate does not act through the pituitary-adrenal axis.

In C3H mice, the females, unlike the males, regularly develop myocardial calcification following prolonged cortisol treatment; ovariectomy offers no protection but testosterone renders females more resistant. In hypophysectomized mice of this strain, neither cortisol nor ACTH produces myocardial calcification.

Nonsteroidal Hormones and Hormone-Like Substances ←

In rats, the osteosclerosis produced by small doses of parathyroid extract is diminished but not prevented by hypophysectomy. From this it was first concluded that STH is not necessary for all types of tissue growth.

The osteitis fibrosa and soft-tissue calcification produced by acute overdosage with parathyroid extract (like that caused by DHT) in the rat is also inhibited by hypophysectomy, although the characteristic hypercalcemia is not markedly affected. Presumably, the pituitary acts mainly by altering the calcium avidity of the organic matrix.

Hypophysectomy partially protects the rat against the production of renal necroses by 5-HT. In hypophysectomized rats, the elevation of the EST, induced by 5-HT is preceded by hyperexcitability.

Steroids ←

Ventura & Selye C24,231/57: In rats, the hyalinosis (nephrosclerosis, myocarditis, polyuria, edema, etc.) produced by chlorocortisol following conditioning by uninephrectomy + NaCl was prevented by hypophysectomy. However, at the same time, the production of pulmonary saprophytosis by chlorocortisol was enhanced. Apparently, in the absence of the hypophysis, the mineralocorticoid activities

are inhibited, whereas the glucocorticoid actions of the same steroid molecule are augmented.

Forchielli et al. D75,874/58: The rate of Δ^4 reduction of 11-desoxycortisol was 3—4-fold greater in female than in male rat liver homogenates and in microsomal fractions containing the $\Delta^4\text{-}5\alpha$ -hydrogenase. Female rat liver contains only one Δ^4 -hydrogenase (5α -microsomal), whereas the male liver contains the soluble $\Delta^4\text{-}5\beta$ -hydrogenase as well. Ovariectomy caused no marked change in enzyme

titer, but hypophysectomy decreased it sharply. Curiously, ACTH, STH, and pregnant mare serum partially restored the enzyme level in the hypophysectomized rat. In young animals, increase in the titer of hepatic $\Delta^4\text{-}5\alpha$ -hydrogenase occurs prior to puberty. This fact (like the negative results after ovariectomy) suggests an independence of enzyme regulation from ovarian hormones.

Lostrøth C54,348/58: Female mice of the C3H strain regularly develop myocardial calcification after prolonged cortisol treatment, whereas males are comparatively resistant. Ovariectomy offers no protection, but testosterone renders females more resistant. In hypophysectomized mice, neither cortisol nor ACTH produces myocardial calcification.

Selye C39,319/58: In rats, nephrocalcinosis produced by excess NaH_2PO_4 p.o. is aggravated by estradiol, but even the severe calcification induced by this combined treatment is prevented by hypophysectomy.

Levin et al. F75,365/67: Phenobarbital increases the 17β -estradiol-metabolizing activity of hepatic microsomal enzymes in immature female rats. The in vitro activity is paralleled by in vivo blockade of the estradiol-induced uterine weight increase. The phenobarbital-induced resistance to the uterine weight-increasing effect of estradiol is not prevented by adrenalectomy or hypophysectomy, indicating that the barbiturate does not act through the pituitary-adrenal axis.

Salgado & Mulroy C84,321/59: In rats, the cardiovascular changes produced by DOC following sensitization by uninephrectomy and NaCl are inhibited by hypophysectomy or thyroidectomy, although not all the lesions are blocked to an equal extent.

Garg et al. G79,002/71: In rats, PCN p.o. induces proliferation of SER even after hypophysectomy.

Szabó et al. G79,024/71: In rats, PCN increases resistance to indomethacin, hexobarbi-

tal, progesterone, zoxazolamine and digitoxin, both in the presence and in the absence of the pituitary. Hypophysectomy also fails to prevent the induction of SER proliferation in the hepatocytes.

Adrenal Cortical Extract ← Hypophysectomy: Zauder B57,611/51*

DOC, Progesterone ← Hypophysectomy: Chamorro A57,215/42*

Estradiol ← Hypophysectomy + Phenobarbital: Levin et al. F75,365/67*

Nonsteroidal Hormones and Hormone-Like Substances ←

Parathyroid Hormone ←. Selye et al. 30,634/34; Thomson et al. A239/34: In rats, osteoblast proliferation and new bone formation following treatment with small doses of parathyroid extract and renal regeneration after uninephrectomy are diminished, yet not completely prevented by hypophysectomy. Apparently, STH is not necessary for all types of growth.

Selye et al. D25,666/62: In the rat, hypophysectomy greatly diminishes both soft tissue calcification and osteitis fibrosa produced by parathyroid extract or DHT. The hypercalcemia is not diminished by the absence of the hypophysis, and the latter may act by altering the metabolism of calcifiable organic matrix.

ACTH, Epinephrine ← Hypophysectomy: Zauder B57,611/51*

5-HT ←. Jasmin & Bois C92,099/60: Hypophysectomy partially protects the rat against the production of renal infarcts by 5-HT. ACTH does not affect this change, cortisol aggravates it, whereas DOC and testosterone offer partial protection.

de Salva D27,783/62: The "EST elevating effect of serotonin and ephedrine in intact rats was preceded by hyperexcitability in hypophysectomized rats."

Drugs ←

Much work has been done on the effect of the hypothalamus-pituitary system on barbiturate resistance.

In rats, thiopental sleeping time is greatly prolonged within two weeks after hypophysectomy. This increased sensitivity is restored towards normal by ACTH, DOC or testosterone. The depressant effect of phenobarbital and of several other muscle relaxants appears to be diminished after hypophysectomy.

The sedative action of hexobarbital and thiopental is diminished by tourniquet stress in intact but not in hypophysectomized or adrenalectomized rats. Various

observations suggest that "the stress effect on the duration of drug action is mediated through increased drug-metabolism." The stimulation of hepatic microsomal hexobarbital and pentobarbital metabolism by the antihistamine, chlorecyclizine, is not prevented in rats by hypophysectomy or by adrenalectomy plus castration; that is, removal of both steroid hormone-producing glands.

X-irradiation of the head considerably enhances the anesthetic effect of thiopental, barbital and pentobarbital in the rat. The induction by phenobarbital of resistance to pentobarbital is not inhibited by cephalic X-irradiation. Irradiation of the head is just as effective as total body irradiation or hypophysectomy in inhibiting the rapid induction of hexobarbital-metabolizing microsomal oxidases by hexobarbital. Even X-irradiation in utero produces the same result. X-irradiation of pregnant rats results in male offspring deficient in hepatic microsomal hexobarbital-metabolizing enzymes, but still capable of responding to phenobarbital with increased enzyme activity. Apparently, "the ontogenetic increase in enzyme activity is hormone-dependent, while that following phenobarbital administration is independent of hormonal regulation as evidenced by the response of hypophysectomized or sexually immature animals." Bilateral electrolytic lesions in the posterior hypothalamus inhibit hepatic hexobarbital oxidase activity in the same manner as does X-irradiation of the head or hypophysectomy.

The hepatic steatosis produced by CCl_4 in rats is less completely prevented by hypophysectomy than by adrenalectomy.

The induction of hepatic damage, and even of hepatomas, by certain carcinogens is inhibited by hypophysectomy in the rat. As judged by the few published observations, certain carcinogens do, whereas others do not, induce hepatic microsomal drug-metabolizing enzymes after hypophysectomy or hypothalamic lesions in the rat.

In rats, hypophysectomy greatly diminishes the skeletal changes produced by lathyrogens, such as AAN. STH restores the ability of the skeleton to react even after hypophysectomy. It is concluded that the normal hormonal secretion of the hypophysis exerts a decisive influence on the development of osteolathyrism.

In weanling male rats, total body X-irradiation inhibits the development of hepatic microsomal enzymes which catalyze the oxidative desulfuration of the pesticide Guthion. Shielding of the liver or testes does not prevent this inhibition, whereas shielding of the head area does. Irradiation did not inhibit enzyme development in hypophysectomized rats. "Thus, the pituitary is necessary for the radiation effect, but involvement of the pituitary is not the result of a radiation-induced deficiency of pituitary hormones."

The nephrocalcinosis produced in rats by oral administration of large amounts of phosphates (e.g., Na_2HPO_4 or NaH_2PO_4) or by HgCl_2 is inhibited by hypophysectomy.

The nephrosis elicited by puromycin aminonucleoside in the rat is not completely prevented by hypophysectomy, but the associated hypercholesterolemia and hyperlipemia are diminished.

Hypophysectomy decreases survival in rats given excessive amounts of vitamin A but does not significantly affect the characteristic skeletal lesions.

Hypophysectomy greatly diminishes the soft-tissue calcification and osteitis fibrosa produced by DHT in rats, but does not significantly affect the associated hypercalcemia. Possibly, the effect of the pituitary is mediated through metabolic changes in the calcifiable matrix. The predominantly cortical nephrocalcinosis pro-

duced by vitamin-D₂ overdosage in the rat is not altered by hypophysectomy. The calciphylaxis elicited by combined treatment with DHT and CrCl₃ is prevented by hypophysectomy in the rat.

Chlorcyclizine shortens the duration of action and increases the hepatic microsomal metabolism of zoxazolamine in male rats. These effects are not prevented by hypophysectomy or adrenalectomy + castration. However, the depressant action of zoxazolamine is diminished after hypophysectomy.

Acrylonitrile

Szabó & Selye G79,010/71: In rats, pretreatment with ACTH (but not with STH) prevents the production of adrenal apoplexy by acrylonitrile. Hypophysectomy protects against adrenal apoplexy, but not against mortality under similar conditions.

Aminopyrine ← Hypophysectomy + Pesticides: Hart et al. G27,102/65

Atropine ←

de Salva D27,783/62: "Atropine and diphenhydramine had no effect in intact rats but produced lowered EST in hypophysectomized rats."

Barbiturates ←

Waltz et al. C11,847/55: In rats, thiopental sleeping time is greatly prolonged within about two weeks after hypophysectomy. This increased sensitivity is restored towards normal by ACTH, DOC, or testosterone.

de Salva D27,783/62: "Drugs with skeletal muscle relaxant properties (phenobarbital, meprobamate, phenaglycodol, mephenesin, and zoxazolamine) were less effective as depressants after hypophysectomy than they were in intact rats."

Rupe et al. E26,910/63: The sedative effect of hexobarbital and thiopental, but not of barbital, was diminished by tourniquet stress, in the intact, but not in the hypophysectomized or adrenalectomized rat. In intact rats, ACTH or cortisone decreases hexobarbital sleeping time, as does stress, whereas SKF 525-A completely blocks the protective action of stress. Presumably "the stress effect on the duration of drug action is mediated through increased drug metabolism."

Conney et al. D52,543/61: Pretreatment of male rats with chlorcyclizine shortens the duration of action and increases the hepatic microsomal metabolism of hexobarbital, pento-

barbital and zoxazolamine. These effects were not prevented by hypophysectomy or adrenalectomy combined with castration.

Bousquet et al. F35,073/65: In rats, stressed by application of a tourniquet to one hind leg, the duration of response to hexobarbital, pentobarbital, meprobamate and zoxazolamine is significantly reduced, but only in the presence of both the pituitary and the adrenal glands. Pretreatment with ACTH or corticosterone simulates the effects of stress in shortening hexobarbital anesthesia. "It is suggested that the pituitary-adrenal axis serves a regulatory function with respect to duration of drug responses which may be mediated by an alteration of drug metabolism."

Nair et al. F53,576/65: In the rat, X-irradiation of the head considerably enhanced the anesthetic effect of thiopental, barbital, and pentobarbital. The induction by phenobarbital of resistance to subsequent pentobarbital anesthesia was not inhibited by cephalic X-irradiation.

Nair & Bau G67,246/67: Exposure of rats to X-irradiation in utero or during early postnatal life suppresses the hexobarbital-metabolizing enzyme system in the liver. Hypophysectomy or irradiation of the head (but not of the body with the head shielded) has a similar effect in adult rats.

Yam & DuBois G58,163/67: In 23-day-old male rats, X-irradiation of the whole animal or the head only inhibited the rapid increase in hexobarbital-metabolizing hepatic microsomal oxidase normally obtained by hexobarbital treatment. Hypophysectomy produced the same result.

Nair et al. G67,245/68: X-irradiation of pregnant rats results in male offspring deficient in the hepatic microsomal enzymes which metabolize hexobarbital. However, irradiation did not suppress the increase of enzyme activity brought about by chemical inducers (phenobarbital). Actinomycin inhibited both the ontogenetic and phenobarbital-induced increases in enzyme activity. "The ontogenetic

increase in enzyme activity is hormone-dependent, while that following phenobarbital administration is independent of hormonal regulation as evidenced by the response in hypophysectomized or sexually immature animals. It is concluded from these results that the inhibitory effect of x-irradiation on the hepatic enzyme system is mediated through an action on the hormonal regulation of enzyme activity."

Nair et al. G67,250/69: Hepatic hexobarbital oxidase activity is inhibited by head X-irradiation, hypophysectomy, or bilateral electrolytic lesions in the posterior hypothalamus. The in vitro data were verified by measurements of the hexobarbital sleeping time. "It is suggested that the microsomal enzyme system metabolizing hexobarbital is normally under the regulatory control of hypothalamo-hypophyseal hormonal activity. The light dependent circadian rhythm for this enzyme, recently reported by us, is also consistent with this interpretation."

Norton G80,572/71: Hypophysectomized rats can become dependent upon barbital and show the same withdrawal symptoms as intact animals. In barbital-dependent rats, the liver, thyroid, adrenals and secondary sex organs are enlarged but the gonads regress. The hepatic enlargement is also evident after hypophysectomy.

Szabó et al. G79,024/71: In rats, PCN increases resistance to indomethacin, hexobarbital, progesterone, zoxazolamine and digitoxin, both in the presence and in the absence of the pituitary. Hypophysectomy also fails to prevent the induction of SER proliferation in the hepatocytes.

Hexobarbital ← Hypophysectomy: Conney et al. D52,543/61; Bousquet et al. F35,073/65*; Yam et al. G58,163/67; Nair et al. H21,083/70*

Benactyzine ←

de Salva D27,783/62: In hypophysectomized rats, the EST elevating effects of reserpine, mescaline, benactyzine and phenyltoloxamine were replaced by an EST lowering action.

Bilirubin ← Hypophysectomy + Barbital, Mouse: Catz et al. H14,471/68

Cadmium ←

Parízek D23,927/60: In rats, cadmium intoxication elicits the usual testicular lesions

even if administered 3 months after hypophysectomy.

Carbon Tetrachloride ←

Furukawa F71,711/65: In rats, hepatic steatosis produced by CCl₄ is inhibited by adrenalectomy and, to some extent, also by hypophysectomy. The effect of CCl₄ after adrenalectomy is restored by corticoids but not by epinephrine which increases only the action of the former. STH does not counteract the effect of hypophysectomy. Alloxan diabetes inhibits CCl₄-induced hepatic lipidosis.

Carcinogens ←

Lacassagne & Nyka 59,016/36: Rabbits, whose pituitary was destroyed by radium, become singularly resistant to the production of papillomas by painting of the ears with benzopyrene or tar.

Korteweg & Thomas A 33,075/39: In mice, hypophysectomy delays but does not prevent the growth of transplanted mammary carcinomas or the induction of cutaneous neoplasms caused by painting the skin with 3:4-benzopyrene.

Moon et al. B74,251/52: In rats hypophysectomized two weeks before s.c. implantation of methylcholanthrene pellets, the development of sarcomas was almost completely prevented.

Griffin et al. B77,163/53: In rats, hypophysectomy inhibits the induction of liver damage and hepatomas by 3-methyl-4-dimethylaminazobenzene (3'-Me-DAB).

Richardson et al. C2,406/53: In rats, hypophysectomy interferes with the production of hepatic cancers by 3'-Me-DAB.

Robertson et al. B88,672/53: In rats, hypophysectomy prevents the production of hepatic cirrhosis and hepatomas by 3'-Me-DAB. The susceptibility to tumorigenesis is restored by ACTH, but not by CON, DOC or testosterone. These hormones likewise failed to prevent carcinogenesis in intact rats.

Richardson et al. B99,907/54: In hypophysectomized rats, 3'-Me-DAB failed to produce hepatomas. Conjoint treatment with ACTH + STH partially restored the carcinogenic activity. Other pituitary preparations, cortisone, testosterone and DOC were ineffective. Earlier literature on the effect of hypophysectomy on carcinogenesis is reviewed.

Robertson et al. E61,212/54: In rats, hypophysectomy inhibits the carcinogenic action of azo dyes. ACTH, STH and, to a lesser

extent, TTH and GTH restored this activity. DOC permitted the development of cirrhosis and bile duct adenomas in carcinogen-treated hypophysectomized females, whereas testosterone and vasopressin were inactive.

Griffin et al. C14,406/55: In rats, the hepatic carcinogenesis normally induced by 3'-Me-DAB is prevented by hypophysectomy, but may be restored by subsequent treatment with either ACTH or STH. The literature on the effect of various hormones upon the induction of neoplasms by carcinogens is reviewed.

Conney et al. D87,867/56: Injection of 3-methylcholanthrene (3-MC) i.p. greatly increases the ability of rat liver homogenates to N-demethylate 3-methyl-4-monomethylaminoazobenzene and to reduce the azo linkage of 4-demethylaminoazobenzene. Neither of these activities was altered after adrenalectomy, but both systems were slightly depressed after hypophysectomy.

O'Neal & Griffin, C31,971/57: In rats, hypophysectomy prevents the induction of hepatomas by 3'-methyl-4-dimethyl-aminoazobenzene. The hepatoma induction by diacetylaminofluorene (DAAF) is also reduced though not abolished by hypophysectomy, but the induction of facial tumors by DAAF is not impeded in the absence of the pituitary. "The development of hepatic neoplasms is apparently regulated by the pituitary gland, while the mechanism of face tumor carcinogenesis by the same compound is independent of this endocrine system."

Huggins et al. C62,178/59: In rats, mammary carcinomas induced by 3-MC involute following ovariectomy or hypophysectomy and, hence, they may be regarded as "hormone-dependent." Similar regression of tumors is frequently achieved by dihydrotestosterone. Only few mammary cancers continue to grow after ovariectomy and these are considered to be "hormone-independent."

In rats, the induction of mammary carcinomas by 3-MC is enhanced during pregnancy, pseudopregnancy, and progesterone treatment. Regression of neoplasms occurs after parturition. Males are virtually resistant. In fully formed tumors, regression could be induced by hypophysectomy or ovariectomy.

Kim & Furth H31,205/60: In rats, the induction of mammary cancers by 3-MC is considerably inhibited by ovariectomy or hypophysectomy. Grafts of functional mammatropic pituitary tumors counteract the inhibitory effect of hypophysectomy in that they not only

stimulate the growth of involuting preexisting cancers, but also cause the appearance of new mammary tumors.

Bielschowsky D10,255/61: In rats, hypophysectomy, thyroidectomy and adrenalectomy inhibit the development of hepatomas by treatment with 2-acetylaminofluorene (AAF) or 2-aminofluorene (AF).

Bock & Dao D11,892/61: In rats, 3-MC accumulation in the mammary glands is increased by hypophysectomy or ovariectomy, but diminished during pregnancy. The affinity of mammary tissue for certain carcinogens may be due to its close association with adipose tissue.

Seguy et al. D5,238/61: In rats, high doses of folliculoids enhanced the carcinogenic action of benzpyrene. Hypophysectomy or ovariectomy did not significantly influence this type of carcinogenesis, but the number of animals used was very small.

Goodall G77,088/62: In rats, the production of hepatomas by AF is prevented by hypophysectomy or thyroidectomy. Cortisone restores the ability of the thyroidectomized but not of the hypophysectomized rats to develop hepatomas after AF treatment. Cortisone strongly accelerates the appearance of hepatomas in intact rats.

Morii & Huggins D45,369/62: In rats, the adrenal necrosis produced by DMBA is prevented by hypophysectomy performed three weeks earlier. ACTH (but not STH) restores the susceptibility of the adrenals in the absence of the pituitary.

Sterental et al. D61,608/63: In rats, mammary tumors induced by DMBA regressed after adrenalectomy + ovariectomy or hypophysectomy. Folliculoid treatment reactivated tumor growth after adrenalectomy + ovariectomy but not after hypophysectomy. These tumors remained unresponsive to folliculoids after hypophysectomy even if thyroid and cortisone replacement therapy was given.

Huggins & Sugiyama F44,582/65: In rats, DMBA produces no adrenocortical necrosis if the animals are immature or hypophysectomized. ACTH renders the adrenals of immature rats susceptible to this type of injury.

Morii G34,628/65: Pretreatment with small amounts of ACTH failed to protect the rat against DMBA-induced adrenocortical apoplexy. However, administration of ACTH to young rats or to hypophysectomized adults, which normally do not respond to the corticolytic effect of DMBA, makes them susceptible.

Shimazu G31,110/65: 20-Methylcholanthrene increases hepatic dimethylaminoazobenzene-demethylase in the rat, even after adrenalectomy, ovariectomy, or hypophysectomy. Hypothalamic lesions decrease the basal level of the enzyme and its response to methylcholanthrene. On the other hand, glutamine synthetase (a microsomal enzyme not induced by methylcholanthrene) is unaffected by hypothalamic lesions.

Huggins & Grand F74,177/66: In rats, neither hypophysectomy nor orchidectomy causes regression of DMBA-induced mammary cancers.

Raitschew G76,731/70: In hamsters, homotransplantation of a pituitary into the kidney increases the number of melanomas produced under standardized conditions by DMBA.

Somogyi G70,416/70: In rats, spironolactone inhibits the adrenocortical necrosis, carcinogenicity and hemopoietic-tissue-damaging action of DMBA. Ethylestrenol, CS-1 and norbolethone are also effective against the DMBA-induced adrenal necrosis. Spironolactone likewise protects against the adrenocortolytic effect of 7-OHM-MBA. Thus, the anti-DMBA action of spironolactone does not seem to be based on the blockade of the transformation of the carcinogen into this supposedly more active metabolite. The preventive action of spironolactone is abolished by ethionine, suggesting the involvement of active protein synthesis. The DMBA-induced adrenal lesions are aggravated by estradiol, testosterone, methyltestosterone, cortisol, triamcinolone, and prednisolone, as well as by the stress of muscular work or restraint. The aggravation of adrenal necrosis by estradiol is diminished but not abolished by hypophysectomy.

Somogyi & Kovacs G60,074/70: In rats, hypophysectomy does not abolish the aggravation of DMBA-induced adrenal necrosis but diminishes its intensity.

Oka & Huggins H36,569/71: In rats, 7,8,12-trimethylbenz(a)-anthracene elicits an erythroblastic leukemia which regresses considerably after hypophysectomy.

Dimethylaminoazobenzene ← Hypophysectomy: Conney et al. D87,867/56; Gelboin et al. D81,074/58*; Shimazu et al. G76,684/59*, G31,110/65

7,12-Dimethylbenz(a)anthracene ← Hypophysectomy: Huggins et al. D13,007/61*; Morii et al. D45,369/62*; Ford et al. D69,790/63*

3-MC ← Hypophysectomy: Moon et al. B74,251/52*; Dao G37,357/64*

Cerium ←

Snyder et al. C99,417/59: In rats, i.v. injection of cerium produced extremely high levels of liver fat in females but not in males. After castration, males reacted as strongly as females. Testosterone reduced fatty infiltration in both intact and ovariectomized females. Hypophysectomy prevented fatty liver formation in both sexes, whereas adrenalectomy did so only in males.

Chlorpromazine ← Hypophysectomy + Chlordanne: Hart et al. G27,102/65

Cycloheximide ←

Fiala & Fiala F33,398/65: In rats, cycloheximide increases microsome-bound hepatic RNA, but this effect is prevented by hypophysectomy.

Digitalis ←

Szabó et al. G79,024/71: In rats, PCN increases resistance to indomethacin, hexobarbital, progesterone, zoxazolamine and digitoxin, both in the presence and in the absence of the pituitary. Hypophysectomy also fails to prevent the induction of SER proliferation in the hepatocytes.

Diphenhydramine ←

de Salva D27,783/62: Diphenhydramine produced lowered EST in hypophysectomized but not in intact rats.

Diphenylhydantoin ←

de Salva D66,177/63: In rats, hypophysectomy decreases the EST raising effect of diphenylhydantoin.

Ephedrine ←

de Salva D27,783/62: The "EST elevating effect of serotonin and ephedrine in intact rats was preceded by hyperexcitability in hypophysectomized rats."

Ergot ←

Messina G18,016/64: In rats, ergotamine produces vascular lesions conducive to tail necrosis more readily in females than in males. Hypophysectomy prevents these toxic manifestations in both sexes, whereas treatment with chorionic gonadotrophin does not affect them.

Hexadimethrine ←

Tuchweber et al. D27,884/63: In rats, hypophysectomy prevents the nephrocalcinosis, but aggravates the adrenal necrosis produced by hexadimethrine. ACTH-treatment of the hypophysectomized rat facilitates the production of nephrocalcinosis, but protects the adrenal. Adrenalectomy prevents this form of nephrocalcinosis even in rats maintained on NaCl or DOC. On the other hand, triamcinolone-treated adrenalectomized rats react to hexadimethrine with strong nephrocalcinosis. Under similar conditions in intact rats, the corticoids did not significantly change the syndrome of hexadimethrine intoxication, except that the anaphylactoid reaction to this compound was inhibited by triamcinolone.

Indomethacin ←

Szabó et al. G79,024/71: In rats, PCN increases resistance to indomethacin, hexobarbital, progesterone, zoxazolamine and digitoxin, both in the presence and in the absence of the pituitary. Hypophysectomy also fails to prevent the induction of SER proliferation in the hepatocytes.

Lathyrogens ←

Selye & Ventura C27,684/57: In rats, hypophysectomy greatly diminished the development of osteolathyrism normally produced by AAN but STH aggravates these bone lesions even more in the absence than in the presence of the pituitary. It is concluded that the normal hormonal secretion of the hypophysis exerts a decisive influence on the development of osteolathyrism.

Selye C31,369/57: Hypophysectomy greatly delays the development of osteolathyrism in rats treated with AAN but simultaneous administration of STH results in bone lesions even more severe than those of intact AAN-treated controls.

Bois et al. E29,177/63: In rats with lathyrism induced by AAN, the increased mitotic rate in the epiphysial cartilages is prevented by hypophysectomy and restored by subsequent STH administration. STH appears to be indispensable for the development of osteolathyrism.

Magnesium ←

Jasmin E7,631/68: In rats, certain manifestations of the magnesium-deficiency syndrome are inhibited by cortisol, hypophysectomy or thyroparathyroidectomy.

Meprobamate ←

de Salva D27,783/62: "(1) Drugs with skeletal muscle relaxant properties (phenobarbital, meprobamate, phenaglycodol, mephenezin, and zoxazolamine) were less effective as depressants after hypophysectomy than they were in intact rats; (2) threshold elevating effects in intact rats of reserpine, mescaline, benactyzine and phenyltoloxamine were replaced by a EST lowering action."

Kato & Vassanelli D40,237/62: "Rats pretreated with phenobarbital, phenaglycodol, glutethimide, nikethamide, chlorpromazine, trifluromazine, meprobamate, carisoprodol, pentobarbital, thiopental, primidone, chlortone, diphenylhydantoin and urethane showed an accelerated metabolism of meprobamate and, at the same time, a diminished duration of sleeping time and paralysis due to meprobamate." SKF 525-A counteracted these actions of the enzyme inducers. In hypophysectomized or adrenalectomized rats, phenobarbital still increased meprobamate metabolism in vitro.

Mercury ←

Szabó & Selye G70,478/70: In rats, hypophysectomy greatly diminishes the nephrocalcinosis produced by $HgCl_2$. This effect of $HgCl_2$ is completely abolished in hypophysectomized rats treated with triamcinolone.

Morphine ←

Tanabe & Cafruny C48,625/58: "The ability of hypophysectomized rats to tolerate large doses of morphine and morphine-withdrawal stresses did not seem to be impaired."

*Morphine ← Hypophysectomy : Zauder B57,611/51**

p-Nitrobenzoic Acid ← Hypophysectomy + Pesticides: Hart et al. G27,102/65

Ozone ←

Fairchild et al. E32,187/63: In rats, hypophysectomy protects against the production of pulmonary edema by ozone inhalation. This effect is not abolished by ACTH or TTH and may be dependent upon the posterior lobe.

Fairchild G71,531/63: Review (6 pp., 26 refs.) on the effect of thyroidectomy, thiourea, thyroid hormones, glucocorticoids and hypophysectomy upon the resistance of various species to inhaled irritants, especially ozone.

Pesticides ←

DuBois et al. B3,089/47: In rats, both insulin and hypophysectomy antagonize the hyperglycemic effect of ANTU, but do not prolong survival.

Hietbrink & DuBois F65,296/66: In weanling male rats, total body X-irradiation inhibits the development of hepatic microsomal-enzyme fraction that catalyzes the oxidative desulfuration of Guthion. Shielding of the liver and testes does not prevent this inhibition, whereas irradiation of the head area—while the remainder of the body is shielded—produces a degree of inhibition similar to that obtained by total body irradiation. “The same dose of irradiation did not inhibit the enzyme development in hypophysectomized weanling rats. Thus, the pituitary is necessary for the radiation effect, but involvement of the pituitary is not the result of a radiation-induced deficiency of pituitary hormones.”

Szabo & Selye G70,497/70: In rats, various catatotoxic steroids, and particularly PCN, offer protection against intoxication with parathion and dioxathion. This protective effect is not prevented by hypophysectomy.

Guthion ← Hypophysectomy + X-irradiation: *Hietbrink et al. F65,296/66*

Phenaglycodol, Phenyltoloxamine ←

de Salva D27,783/62: “(1) Drugs with skeletal muscle relaxant properties (phenobarbital, meprobamate, phenaglycodol, mephenesin, and zoxazolamine) were less effective as depressants after hypophysectomy than they were in intact rats; (2) threshold elevating effects in intact rats of reserpine, mescaline, benactyzine and phenyltoloxamine were replaced by a EST lowering action.”

Phosphates ←

Selye et al. C16,047/56: In rats, hypophysectomy inhibits the development of nephrocalcinosis after the administration of large amounts of Na_2HPO_4 p.o. or of NaH_2PO_4 by the “granuloma-pouch” technique. However, the atrophy of the outer renal cortex, induced by repeated injections of hypertonic phosphate solutions into the granuloma pouch, is not prevented by hypophysectomy.

Selye C39,319/58: In rats, nephrocalcinosis produced by excess NaH_2PO_4 p.o. is aggravated by estradiol, but even the severe calcification induced by this combined treatment is prevented by hypophysectomy.

Puromycin Aminonucleoside ←

Oliver & Kelsch F25,772/64: In rats, the development of the nephrotic syndrome produced by puromycin aminonucleoside (PAN) is not prevented by hypophysectomy.

Hoak et al. F61,136/65: In rats with nephrosis induced by PAN the usual hypercholesterolemia and hyperlipemia are inhibited by hypophysectomy.

Reserpine ←

de Salva D27,783/62: In hypophysectomized rats, the EST-elevating effects of reserpine, mescaline, benactyzine and phenyltoloxamine were replaced by an EST-lowering action.

Efron D59,758/62: In rats, adrenalectomy greatly decreases resistance to reserpine, whereas hypophysectomy leaves it almost unchanged. It is assumed therefore, “that the increased toxicity of reserpine in adrenalectomized rats is related to the absolute lack of certain adrenal steroids, which in some way may condition the nervous system to the effects of the drugs, rather than to the inability of the pituitary-adrenal system to respond to so-called ‘nonspecific stress’ caused by the drug.”

Strychnine ← Hypophysectomy: *Kato et al. G74,030/62*

Vitamin A ←

Wolbach & Maddock B83,297/52: In rats, hypophysectomy decreases survival during vitamin-A overdosage, but does not significantly affect the skeletal response characteristic of this type of hypervitaminosis, except that bone repair processes are inhibited.

Vitamin D, DHT ←

Selye et al. D20,710/62: In rats, hypophysectomy greatly inhibits the development of calciphylaxis following combined treatment with DHT + CrCl_3 .

Selye et al. D25,666/62: In the rat, hypophysectomy greatly diminishes both soft tissue calcification and osteitis fibrosa produced by parathyroid extract or DHT. The hypercalcemia is not diminished by the absence of the hypophysis and the latter may act by altering the metabolism of calcifiable organic matrix.

Bekemeier & Leiser D65,289/63: Vitamin-D₂ overdosage produces predominantly cortical nephrocalcinosis in intact, adrenalectomized, or hypophysectomized rats. Additional treatment with dienestrol (an artificial folliculoid)

shifts calcium deposition predominantly to the cortico-medullary junction, irrespective of the presence or absence of the hypophysis or adrenals.

Water ← Hypophysectomy, Dog:
Bodo et al. 88,791/45*

Zoxazolamine ←

Conney et al. D52,543/61: Pretreatment of male rats with chlorcyclizine shortens the duration of action and increases the hepatic microsomal metabolism of hexobarbital, pentobarbital and zoxazolamine. These effects were

not prevented by hypophysectomy or adrenalectomy combined with castration.

de Salva D27,783/62: "(1) Drugs with skeletal muscle relaxant properties (phenobarbital, meprobamate, phenaglycodol, mephenesin, and zoxazolamine) were less effective as depressants after hypophysectomy than they were in intact rats."

Szabó et al. G79,024/71: In rats, PCN increases resistance to indomethacin, hexobarbital, progesterone, zoxazolamine and digitoxin, both in the presence and in the absence of the pituitary. Hypophysectomy also fails to prevent the induction of SER proliferation in the hepatocytes.

***Microorganisms, Bacterial Toxins and Venoms* ←**

Hypophysectomy greatly diminishes the resistance of the rat to tuberculosis and this induced susceptibility can be abolished by STH. In guinea pigs, hypophysectomy reduces resistance even to the toxic actions of killed tubercle bacilli, a defect which cannot be corrected by DOC or cortisone. After hypophysectomy, cortisone is even more effective in protecting mice against endotoxin shock than in the presence of the pituitary, but reserpine fails to block endotoxin shock after hypophysectomy. It has been claimed, however, that resistance to endotoxin is actually increased a few hours after hypophysectomy or adrenalectomy in the mouse. The low endotoxin resistance of hypophysectomized rats is not corrected by parabiosis with an intact partner.

The resistance of the rat to cobra venom is reduced by about 2/3 after hypophysectomy.

Tuberculosis ←

Steinbach et al. B7,316/44: In rats, hypophysectomy greatly diminishes resistance to experimental tuberculosis.

Tonutti & Fetzer B75,190/52: In guinea pigs, hypophysectomy greatly reduces resistance to the toxic actions of killed tubercle bacilli. This defect is uninfluenced by DOC, but abolished by cortisone, although the latter accelerates dissemination of living tubercle bacilli.

Gillissen & Busanny-Caspari C6,858/53: In guinea pigs and rabbits, hypophysectomy did not significantly influence the course of tuberculosis [Only three animals of each species were used (H.S.).]

Bisetti & Barbolini D12,624/61: Rats which are normally highly resistant to infection with tuberculosis bacilli, become sensitive after hypophysectomy. This induced

susceptibility can be abolished by STH. To a much lesser extent ACTH also offers some protection.

***Bacterial Toxins* ←**

Chedid & Parant D6,761/61: The protection of intact mice against endotoxin shock by cortisone is inhibited by reserpine. The same is true in adrenalectomized rats, whereas after hypophysectomy cortisone is even more effective in offering protection against endotoxin, but reserpine no longer blocks this effect. Apparently the drug interferes with the cortisone effect only in the presence of the pituitary.

Parant D82,116/62: In mice, resistance to endotoxin is greatly increased a few hours after adrenalectomy or hypophysectomy. Cortisone protects normal, adrenalectomized, and hypophysectomized animals against high

doses of endotoxin, whereas chlorpromazine is effective only in the presence of both the adrenals and the pituitary. ACTH also protects the hypophysectomized mouse but only if slow absorption is assured.

Chedid et al. D57,924/63: The low resistance of hypophysectomized rats to endotoxin

is not corrected by parabiosis with an intact partner.

Venoms ←

Ball & Samuels 7,404/32: In rats, hypophysectomy is estimated to diminish resistance to cobra venom to about 2/3 of the norm.

Immune Reactions ←

In rats, hypophysectomy does not significantly modify antibody production after treatment with various antigens. On the other hand, fatal anaphylactic shock can be produced in hypophysectomized, but not in intact, rats. In guinea pigs, anaphylactic reactivity can be suppressed by anterior hypothalamic lesions, perhaps through their effect upon adrenal and thyroid secretion.

Hepatic and Renal Lesions ←

In rats and mice, hypophysectomy does not abolish the increase in hepatic polyplioidy which occurs after partial hepatectomy, but it diminishes mitotic regeneration of the liver. This defect is corrected by STH, but further aggravated by cortisone.

Renal regeneration after partial nephrectomy is inhibited, but not abolished, by hypophysectomy in the rat. This observation first called attention to the fact that STH is not necessary for all types of growth.

The compensatory hypertrophy of the remaining kidney following uninephrectomy is diminished, but not abolished, by hypophysectomy in the rat and dog. However, if hypophysectomy precedes uninephrectomy by 15 days, the inhibition of regeneration is much less evidently suppressed. Presumably by that time, involution of the kidneys is already so pronounced that even mild compensatory hypertrophy is proportionately more evident. However, if hypophysectomy is performed two weeks after uninephrectomy, it causes severe involution of the remaining kidney.

Immune Reactions ←

Molomut 76,648/39: In rats, hypophysectomy does not significantly modify antibody production after treatment with various antigens. On the other hand, fatal anaphylactic shock could be produced in hypophysectomized but not in intact rats, though both groups of animals presented a similar antibody picture.

Filipp & Mess G71,129/69: In guinea pigs, suppression of anaphylactic reactivity by anterior hypothalamic lesions can be partially blocked by chronic treatment with thyroid hormones as well as by adrenalectomy or adrenal inactivation by metyrapone (Metopiprone). "Combined treatment of guinea pigs bearing hypothalamic lesions with Metopiprone

and thyroxine completely eliminated the blocking effect of the tuberal lesion on anaphylactic reactions." Apparently the shock-inhibiting effect of hypothalamic lesions is partly due to hypothyroidism and partly to hypoadrenalcorticoidism.

Hepatic Lesions ←

Canzanelli et al. B37,729/49: In rats, hypophysectomy delays liver regeneration after partial hepatectomy but "neither adrenalectomy nor the administration of adrenal cortex extract has any effect on the amount of liver regeneration."

Christensen & Jacobsen A 49,204/49: In rats subjected to partial hepatectomy, neither hypophysectomy nor thyroidectomy impairs

the rate of regeneration. No significant change in mitotic rate was observed after pretreatment with stilbestrol or STH.

Hemingway & Cater C56,780/58: In rats subjected to hypophysectomy + partial hepatectomy, mitotic regeneration of the liver is inhibited. Cortisone further inhibits mitosis and causes nuclear degeneration. These changes can in turn be blocked by treatment with STH.

Weinbren D95,941/59: Review (11 pp., 110 refs.) and personal observations on factors influencing hepatic regeneration after partial hepatectomy in the rat, with special sections on the effects of hypophysectomy and thyroid hormones.

Bucher G68,621/63: Review on the influence of hypophysectomy and hypophysial hormones upon hepatic regeneration.

Swartz G53,670/67: Studies in rats and mice on the increase in hepatic polyploidy after partial hepatectomy. In the rat, hypophysectomy does not abolish polyploidization.

***Renal Lesions* ←**

Selye et al. 30,634/34: In rats, osteoblast proliferation and new bone formation following treatment with small doses of parathyroid extract and renal regeneration after uninephrectomy are not prevented by hypophysectomy. Apparently, STH is not necessary for all types of growth.

Gonzalez 79,025/38; A34,057/38: In toads, hypophysectomy diminishes compensatory renal hypertrophy following uninephrectomy. This defect can be partially compensated by either anterior- or posterior-pituitary implants.

McQueen-Williams & Thompson A33,938/40: In rats, total hypophysectomy prevented the compensatory hypertrophy of the remaining kidney after uninephrectomy. Thyroidectomy did not prevent renal regeneration under identical conditions.

Winternitz & Waters A34,910/40: In dogs, hypophysectomy almost completely prevents

compensatory hypertrophy of the remaining kidney after uninephrectomy.

Braun-Menendez & Houssay B45,945/49: In rats, the compensatory hypertrophy of the remaining kidney following uninephrectomy is diminished but not abolished by hypophysectomy. The earlier literature on this topic is reviewed.

Astarabadi & Essex B75,446/52: In dogs, hypophysectomy diminishes, but does not completely abolish, compensatory hypertrophy of the remaining kidney after uninephrectomy.

Astarabadi & Essex B86,411/53: In dogs, the inhibition of compensatory renal hypertrophy following uninephrectomy is largely overcome by treatment with lyophilized anterior pituitary extract. In rats, hypophysectomy is less effective in inhibiting compensatory renal hypertrophy but treatment with pituitary extract fails to restore normal renal growth after hypophysectomy and uninephrectomy.

Sandri et al. C13,150/55: In rats, compensatory hypertrophy of the remaining kidney after uninephrectomy is greatly inhibited by hypophysectomy if the two operations are performed simultaneously, but not if hypophysectomy precedes uninephrectomy by 15 days. [Presumably by that time, involution of the kidneys is already so pronounced that even mild compensatory hypertrophy is proportionately more evident (H.S.).]

Astarabadi D8,815/61: In rats, hypophysectomy performed two weeks after uninephrectomy caused involution of the remaining kidney. "The results of the experiment suggest the presence of a renotropic principle in the hypophysis which is required for the compensatory renal hypertrophy." [At the time of hypophysectomy, compensatory hypertrophy was virtually complete, hence, the experiment merely confirms that hypophysectomy causes renal involution, a fact previously established on intact rats (H.S.).]

***Various Stressors* ←**

In rats, resistance to total body X-irradiation is considerably decreased after hypophysectomy, although the characteristic polyuria and polydipsia of the first few days are diminished. The tendency to develop duodenal lesions under the influence of X-irradiation is not considerably altered by hypophysectomy in the rat, and ACTH does not consistently ameliorate the irradiation syndrome in the absence of the pituitary.

In hypophysectomized rats, sensitivity to cobalt irradiation is increased by testosterone and estradiol.

Goldfish also become unusually sensitive to X-irradiation after hypophysectomy.

Resistance to increased oxygen tension is enhanced by hypophysectomy, presumably because the thyroid function is diminished; administration of desiccated thyroid or thyroxine restores the high oxygen resistance of the hypophysectomized rat to normal.

Resistance to cold is decreased after hypophysectomy in the rat, but restored towards normal by cortical extract, ACTH, or TTH.

The EST is lowered in rats by hypophysectomy as it is by thyroidectomy or adrenalectomy.

The growth of Walker tumor transplants is essentially normal in hypophysectomized rats maintained on cortisol + DOC.

Ionizing Rays ←

Tyree et al. B33,116/48; Patt et al. B33,711/48: In rats, hypophysectomy decreases resistance to total body X-irradiation.

Smith & Tyree C12,045/56: In rats, the polydipsia and polyuria seen during the first days after X-irradiation tend to be inhibited by adrenalectomy or hypophysectomy.

Baker et al. C56,998/58: In rats, hypophysectomy does not significantly alter the duodenal lesions produced by total body X-irradiation.

Ghys D70,483/62: In hypophysectomized rats, sensitivity to cobalt irradiation is greatly increased by testosterone and estradiol.

Grafov D20,890/62: In rats, the decreased resistance to total body X-irradiation induced by hypophysectomy is not consistently ameliorated by ACTH.

Etoh & Egami G11,664/63: In goldfish, resistance to X-irradiation is greatly diminished both by adrenalectomy and by hypophysectomy.

Hyperoxygenation ←

Bean & Johnson B68,165/52: In rats exposed to oxygen under high pressure, resistance was increased by hypophysectomy.

Bean & Bauer B76,951/52: In rats, desiccated thyroid augments the adverse effects of exposure to high oxygen tension. It also abolishes the protective effect of hypophysectomy.

Smith et al. C95,244/60: In rats, desiccated thyroid or thyroxine increases the noxious effects of breathing virtually pure oxygen at atmospheric pressure. Conversely, hypophysectomy increases resistance to oxygen presumably through the elimination of TTH.

Temperature Variations ←

Baird et al. 14,881/33: In rats, resistance to cold is greatly diminished after hypophysectomy but restored by cortical extract, TTH or thyroxine.

Tyslowitz & Astwood 80,678/41: In hypophysectomized rats, the decreased resistance to cold is largely corrected by ACTH and adrenocortical extract. In adrenalectomized rats, adrenocortical extract is also effective in this respect, whereas ACTH is not.

Electric Stimuli ←

de Salva D66,176/63: In rats, the EST is reduced in descending order of magnitude by adrenalectomy, hypophysectomy and thyroidectomy. The effect of these endocrine deficiencies upon various depressant drugs is also described.

de Salva et al. C51,842/58: In rats, the EST was lowered by hypophysectomy and adrenalectomy, but only insignificantly by thyroidectomy. 5-HT elevated the EST.

de Salva D66,177/63: In rats, hypophysectomy decreases the EST raising effect of diphenylhydantoin.

Gispen et al. G77,128/70: In rats exposed to unescapable electric shock the threshold for flinch, jerk, run and jump was significantly lowered by hypophysectomy. ‘Treatment with the ACTH analogue ACTH₁₋₁₀ did not affect threshold levels in hypophysectomized or intact rats. It is concluded that the stimulating effect of ACTH₁₋₁₀ on conditioned-avoidance acquisition in hypophysectomized rats is not caused by an influence on sensory capacities.’

Tumors ←

Korteweg & Thomas A 33,075/39: In mice, hypophysectomy delays but does not prevent the growth of transplanted mammary carcinomas or the induction of cutaneous neoplasms caused by painting the skin with 3:4-benzopyrene.

Ventura et al. C 23,299/57: In rats, the growth of transplanted Walker tumors is essentially normal after hypophysectomy and maintenance therapy with cortisol + DOC. However, the tumor cachexia is greatly increased, whereas the severe involution of the spleen and liver, as well as the development of leukemoid tissue infiltrates in the adrenals and spleen were inhibited.

Hepatic Enzymes ←

For the extensive literature concerning the effect of hypophysectomy on the basic levels of hepatic TPO, TKT, GOT, and other enzymes, as well as upon induction of such enzymes by hormones or substrates, cf. the Abstract Section.

TPO, TKT ←

Geschwind & Li B 95,517/53: Hypophysectomy does not abolish (and perhaps even increases) the resting TPO activity of the rat liver. However, in hypophysectomized animals, the ability to induce this enzyme by tryptophan injection is gradually diminishing during the first 14 post-operative days. Treatment with ACTH enhances the formation of this adaptive enzyme system (measured by kynurenin formation) even without treatment with tryptophan.

Geschwind & Li B 93,277/54: In the rat, the induction of the TPO enzyme system is diminished by hypophysectomy and adrenalectomy, but increased by thyroidectomy.

Thomson & Mikuta B 90,975/54: "Total-body X-irradiation produces within a few hours a dose-dependent increase in the TPO system of rat liver. The increase does not occur in adrenalectomized rats, and hence cannot be construed as a direct effect of X-irradiation." After hypophysectomy, enzyme induction became progressively less pronounced as adrenal atrophy developed. ACTH restored the ability of the hypophysectomized rat to respond with enzyme induction.

McCann et al. E 93,864/59: In rats, hypothalamic lesions interfering with ACTH-secretion, as well as hypophysectomy decrease the induction of hepatic TPO by histidine, but do not block the response completely.

Maickel & Brodie C 83,071/60: TPO in rat liver is increased by ACTH, cortisone, or cortisol, as well as by various stressor agents and barbiturates. Hypophysectomy prevents the effect of stressors and barbiturates, suggesting

that the latter act through the pituitary-adrenal system.

Westermann et al. C 83,072/60: In the rat, large doses of reserpine produce an alarm reaction with an increase in the hepatic TPO activity associated with lowered brain serotonin and norepinephrine. Hypophysectomy prevents these responses.

Rosen & Milholland D 23,053/62: Administration of L-tryptophan, but not of tyrosine, stimulated hepatic TKT activity in adrenalectomized rats. No such induction was obtained by tryptophan in vitro. Adrenalectomized rats treated with tyrosine, methionine or histidine had slightly subnormal TKT levels. Tryptophan analogues (D-tryptophan, acetyl-L-tryptophan, indole, D,L-5-OH-tryptophan and 5-HT), increase both TKT and TPO activity in the livers of adrenalectomized rats. In hypophysectomized rats, tryptophan, 5-HT or 5-OH-tryptophan caused only a slight rise in the hepatic activity of TPO or TKT.

Rosen & Milholland E 32,652/63: Tryptophan induced significant increases in hepatic TKT activity in intact and in adrenalectomized (NaCl-maintained) rats. Tyrosine, histidine and methionine slightly depressed the hepatic TKT activity of the adrenalectomized rats. Analogues of tryptophan (including D-tryptophan, acetyl-L-tryptophan, indole, DL-5-hydroxytryptophan and 5-HT i.p.) increase both TKT and TPO activity by 50—300% in the livers of intact or adrenalectomized rats. 5-HT and DL-5-hydroxytryptophan were most active. After hypophysectomy, the response of each of these enzymes to tryptophan gradually diminished. After 6 months, tryptophan, 5-hydroxytryptophan

and 5-HT failed to cause significant increases in the hepatic activity of these enzymes, but cortisol remained highly effective, causing increases in both enzyme activities comparable to those seen in intact or adrenalectomized rats. "Experiments with two known inhibitors of protein synthesis, DL-ethionine and puromycin, indicate that a major fraction of the induced activity of tryptophan pyrolase seen in adrenalectomized or hypophysectomized rats treated by injection with tryptophan is due to activation rather than synthesis of new enzyme protein. The responses of tryptophan pyrolase and tyrosine transaminase in liver following cortisol administration appear to be mainly the result of the synthesis of each of these enzymes."

Nomura et al. G33,405/65: Various forms of stress (forced exercise, immobilization, cold), as well as the administration of chlorpromazine, increased the TPO-activity of the liver both in intact and in adrenalectomized, but not in hypophysectomized, rats.

Kenney & Albritton G64,557/65: Review of the literature suggesting that transaminase induction in response to stressors can be interpreted as due to corticoid secretion during the stress reaction. Cortisol increases enzyme synthesis following an increased rate of ribosomal transfer synthesis and "DNA-like" RNA's. The present experiments confirm the view that repressor(s) can inhibit enzyme synthesis at the translational level because inhibition of RNA synthesis can prolong the corticoid-induced increase in enzyme synthesis under suitable conditions. "Administration of stressing agents (tyrosine, Celite) to adrenalectomized rats initiates a highly selective repression of the synthesis of hepatic tyrosine- α -ketoglutarate transaminase. The enzyme level falls with a $t_{1/2}$ of about 2.5 hr. Immunological measurement of the rate of enzyme synthesis indicates that it is reduced essentially to zero in stressed, adrenalectomized rats, whereas labeling of total liver soluble proteins is unaffected. Actinomycin does not itself influence the enzyme level, but it blocks the stress-initiated repression of enzyme synthesis, indicating that repression acts at the translational level, whereas initiation of repression involves transcriptional processes." In hypophysectomized rats, stressors are ineffective and preliminary data suggest that STH is responsible for transaminase repression.

Fiala & Fiala F65,983/66: In the rat, cycloheximide (Actidione) i.p. inhibits the synthesis of hepatic TPO assayed 4 hrs after

administration of the substrate, or of cortisol. By contrast, actidione did not abolish the induction of TKT by cortisol and, in fact, actidione increased the level of TKT even in the absence of cortisol treatment. A similar, though smaller, effect occurred in hypophysectomized or adrenalectomized rats, suggesting a direct induction of TKT by actidione. Puromycin inhibited the synthesis of TKT. Apparently, an inhibitor of protein synthesis such as actidione may also act as an inducer for the synthesis of TKT, thus simulating the action of cortisol. "This 'pseudohormonal' action of actidione may explain the toxicity of actidione in certain mammalian species and also the fact that hydrocortisone may act as an antidote in actidione poisoning. It does not explain why a similar effect of 'pseudohormonal' induction is not observed in the case of TPO, but only the inhibition of enzyme induction."

Schapiro et al. F67,227/66: Hepatic TKT-activity increased in immature, stressed (reciprocating shaker) rats, whereas intact stressed adults showed no change. In the stressed adrenalectomized adults, TKT activity markedly decreased, while adrenalectomized immature rats showed no change. Hypophysectomy largely abolished inhibition in the adults. TPO-activity, when present, was increased by stress in old-age groups, but the increase was abolished by adrenalectomy and hypophysectomy. "The results suggest stress-activation of a pituitary mechanism that inhibits or represses activation of tyrosine transaminase and that may not function during early postnatal life."

Grossman & Mavrides G46,206/67: Studies on the kinetics of cortisol-induced hepatic TKT activity in adrenalectomized rats. "Puromycin inhibited enzyme synthesis when it was given during the initial phase of induction. However, it unexpectedly caused a rapid reappearance of enzyme activity following its administration during the inactivation phase. This potentiated response is consistent with other observations which lead to the idea that a repressor is formed about 4 hours after hormone administration and that inhibition of repressor synthesis allows, at least temporarily, continued synthesis of enzyme." The inactivator appears to depend upon pituitary function, since adrenalectomized and hypophysectomized rats showed little or no inactivation phase following cortisol treatment.

Kenney G50,810/67: In intact, hypophysectomized or adrenalectomized rats, STH inhibits the synthesis of hepatic TKT. The

rate of enzyme synthesis is reduced nearly to zero (immunochemical-isotopic analyses), whereas labeling of the bulk of the liver proteins is increased by STH. Repression is blocked when RNA synthesis is inhibited by actinomycin. STH also appears to play a role in the repression of TKT induction by stressors. A hypophysectomized and an intact rat were united by parabiosis. When the pituitary-bearing member was stressed by tyrosine i.p., repression occurred in the livers of both treated and untreated (hypophysectomized) animals. Transaminase levels were unchanged in a single experiment where the stressing agent was administered to the hypophysectomized partner.

Labrie & Korner G56,018/68: The basal level of TPO and TKT was unchanged in the liver of the hypophysectomized rat, but injected cortisol produced greater increases in these enzyme activities. STH depressed these enzyme activities only after pretreatment for four days in either hypophysectomized or adrenalectomized rats, but even shorter pretreatment counteracted the enzyme-inducing effect of cortisol. An amino-acid mixture p.o. enhanced cortisol stimulation of both enzyme activities and abolished the STH-inhibition of the cortisol effect.

Govier & Lovenberg G70,841/69: In rats, the increase in hepatic TKT produced by phentolamine is almost completely abolished by adrenalectomy or hypophysectomy. If small doses of cortisol are given to adrenalectomized rats, phentolamine again increases enzyme activity. Aminoglutethimide completely eliminates both the increase in plasma corticosterone and enzyme induction by phentolamine. "It is concluded that at least two factors are operative in the induction of TKT by phentolamine—(1) a response to an increased plasma corticosterone concentration, and (2) an additional effect which may be a direct substrate type of induction."

Lane & Mavrides H12,953/69: Cortisol caused a greater increase of hepatic TKT in hypophysectomized than in adrenalectomized rats. In general, elevation of enzyme activity after cortisol was inversely proportional to the initial enzyme level, and the latter was in turn higher on protein-rich than on protein-poor diets.

Geller et al. H8,414/69: The stress of laparotomy increases hepatic TKT activity in intact, but not in the adrenalectomized rat, which actually responds in an inverse manner. Hypophysectomy eliminates some, but not

all, of this laparotomy-induced repression. Under these conditions, the TPO- and the TKT-responses are somewhat different.

GPT, GOT ←

Beaton et al. C10,012/55: STH decreases the hepatic GPT and d-amino acid oxidase activity in nonpregnant female rats. These effects are even more pronounced if the animals receive STH + "equine estrogenic substances" + progesterone. This enzyme activity also decreases during pregnancy both in intact and in hypophysectomized rats.

Rosen et al. C50,741/58: In rats treated with cortisol, cortisone or prednisone for 1 week, there was an increase in hepatic GPT but not in GOT. DOC had no such effect. Hypophysectomy or adrenalectomy did not prevent this action of cortisone. STH, testosterone or insulin failed to alter GPT activity nor did they influence its stimulation by cortisol.

Rosen et al. C71,414/59: Marked increases in GPT activity were observed in the livers of rats given cortisol, cortisone, 9 α -fluorocortisol, prednisone, 6 α -methylprednisolone, 9 α -fluoro-21-desoxy-6 α -methylprednisolone or ACTH, whereas two nonglucocorticoid cortisol derivatives, 11-epicortisol and 9 α -methoxy-cortisol, were inactive. STH, testosterone and insulin caused no significant change in GPT by themselves nor did they modify the action of cortisol. On the other hand, large doses of estradiol and thyroxine caused a moderate increase in GPT activity but when injected simultaneously with cortisol they appeared to interfere with its action as did progesterone. Adrenalectomy slightly diminished or failed to affect the GPT inducing activity of cortisol, whereas hypophysectomy caused a rise in GPT activity and augmented the effect of cortisol.

Harding et al. D14,355/61: In the rat, pretreatment with DOC depresses the hepatic GPT activity. A similar depression is obtained by adrenalectomy, but this is not further aggravated by concurrent treatment with DOC. ACTH increases alanine transaminase activity in hypophysectomized, but not in adrenalectomized, animals. In hypophysectomized rats, DOC fails to lower alanine transaminase, nor does it alter the response of this enzyme to ACTH. "The inhibitory effect of DOC on alanine transaminase activity appears to be due to suppression of ACTH release by the pituitary."

Other Amino Acid Enzymes ←

Zuchlewski & Gaebler D91,862/57: Hepatic glutamic acid dehydrogenase activity increases after hypophysectomy in the rat, and is not altered by STH either in hypophysectomized or in sham-operated control animals. GPT and GOT activities have also been investigated under similar conditions.

Freedland & Avery G67,766/64: In the rat, the TDH and SDH activity of liver homogenates was increased by high protein diets, alloxan diabetes, or cortisol. Factors affecting the activity of TDH caused a proportional change in SDH suggesting that both of these activities may be due to a single protein. The SDH activity was decreased by adrenalectomy or hypophysectomy. Adrenalectomy had no effect upon the response of this enzyme to protein feeding, whereas, after hypophysectomy, this response was diminished.

Freedland G28,270/65: Hypophysectomy causes a marked decrease in the hepatic microsomal arginase and arginine synthetase activity in the rat, and both these urea-cycle enzyme levels are increased by cortisol and high-protein diet, even after hypophysectomy.

Ishikawa et al. F41,763/65: In alloxan-diabetic rats, the hepatic SDH and TDH activities are greatly increased. SDH was readily induced by cortisol in the diabetic, but not in the normal, rat. The effects of actinomycin S, STH, and starvation upon SDH have also been studied in intact, hypophysectomized, adrenalectomized and thyroidectomized rats. It is concluded that "serine dehydratase activity in the liver plays an important role in the production of pyruvate as a starting material for gluconeogenesis."

Shimazu G31,110/65: 20-Methylcholanthrene increases hepatic dimethylaminoazobenzene-demethylase in the rat, even after adrenalectomy, ovariectomy, or hypophysectomy. Hypothalamic lesions decrease the basal

level of the enzyme and its response to methylcholanthrene. On the other hand, glutamine synthetase (a microsomal enzyme not induced by methylcholanthrene) is unaffected by hypothalamic lesions.

Various Enzymes ←

Greengard et al. D12,966/61: Hypophysectomy enormously increases the rise in hepatic DPN content induced by nicotinamide i.p. in the rat. ACTH or cortisone suppresses this increase. Many of the metabolic actions of the pituitary-adrenal system may depend upon alterations in the hepatic concentration of this coenzyme.

Abraham et al. G20,214/64: Hypophysectomy drastically reduces the citrate-cleavage enzyme activity induced in rat liver by dietary measures.

Dietrich & Yero G26,959/65: Cortisol markedly lowered the nicotinamide deamidase activity of the liver in intact, hypophysectomized, and adrenalectomized rats. Under these conditions, cortisol failed to inhibit hepatic synthesis of NAD significantly after nicotinamide challenge. Hexestrol markedly lowered hepatic deamidase activity in intact, thyroidectomized, and adrenalectomized rats. A lowering of the hepatic NAD-levels after nicotinamide challenge occurred upon hexestrol treatment in intact, but not in adrenalectomized, rats. Hypophysectomy markedly stimulated nicotinamide deamidase activity and NAD-biosynthesis after nicotinamide challenge.

Freedland et al. G55,808/68: Extensive studies on the effect of adrenalectomy, hypophysectomy and cortisol treatment upon a great variety of rat liver enzymes, with observations on the effect of thyroxine upon these enzymes in intact, adrenalectomized or hypophysectomized rats. The extensive data do not lend themselves to succinct presentation in the form of a summary and must be consulted in the original.

← ***THYROID HORMONES***

The role of the thyroid in resistance, and particularly in drug detoxication, is very great but poorly understood. The discovery by Reid Hunt, at the beginning of this century, that thyroid extract increases the acetonitrile resistance of the mouse was probably one of the first clear-cut demonstrations in the field of hormone-induced drug resistance. The "Hunt test" was so sensitive and reliable that it has been widely used for bioassay purposes, although the underlying mechanism remains mysterious even today.

As we shall see from the following pages, thyroid deficiency and hyperthyroidism alter reactivity to innumerable agents, including hormones, drugs, infections, stressors, and particularly exposure to temperature variations. In all these cases, it is of course tempting to hold changes in the BMR responsible for altered resistance, since a general increase or decrease in metabolism affects the activity of most chemical reactions, be they favorable or detrimental to the organism. However, recent work on the catatoxic steroids indicates that thyroid hormones can significantly influence the activity of the hepatic microsomal drug-metabolizing enzymes and through them the degradative inactivation of toxicants or, conversely, their transformation into metabolites even more toxic than the parent compounds.

Despite the voluminous literature described in the following pages, no systematic study has as yet been carried out along these lines. The exploration of the part played by the thyroid hormones in resistance appears to be particularly promising now against the background of what we have learned recently about the corresponding actions of steroids.

Steroids ←

Corticoids ←. The nephrosclerosis produced by DOC + uninephrectomy + NaCl in the rat is greatly aggravated by thyroxine. Thyroidectomy has an inverse effect, although not all the lesions are equally affected by it. The glycogenolytic action of thyroid feeding is counteracted by cortisone. Thyroxine increases the toxicity of many drugs (e.g., digitoxin, indomethacin, nicotine, phenindione, various pesticides) against which ethylestrenol offers excellent protection. The protective effect of catatoxic steroids can be counteracted by concurrent treatment with thyroid hormone.

Testoids ←. It has been claimed that in orchidectomized mice, thyroxine increases the seminal vesicle enlargement produced by testosterone. In rats, the renotrophic action of methyltestosterone is enhanced by thyroxine.

Folliculoids ←. The hypercalcemia produced in cockerels by stilbestrol is inhibited by thyroxine, and the oviduct stimulating effect of estradiol in young pullets is increased by thiouracil.

In ducks, estradiol stimulates the proliferation of fine spongy bone trabeculae. Thyroidectomy retards bone proliferation, whereas conjoint treatment with thyroxine and estradiol leads to the abundant formation of thick trabeculae.

In rats, thyroidectomy diminishes, whereas thyroid extract increases the hepatotoxicity of CCl_4 .

Corticoids ← cf. also Selye B40,000/50, p. 552; C92,918/61, p. 280; G60,083/70, pp. 326, 401.

Selye et al. B229/45: In rats, the nephrosclerosis produced by DOC after uninephrectomy + NaCl is greatly aggravated by thyroxine.

Kusama C58,473/57: In rats, the glucagonolytic action of thyroid feeding is counteracted by cortisone.

Yates et al. C51,744/58: Studies on the Ring A reduction of cortisone by slices and homogenates of rat livers after pretreatment

with thyroxine or previous thyroparathyroidectomy showed that the total hepatic activity is less in normal males than in females. "Activity was increased 37% and 45% in hyperthyroid males and females respectively, and was decreased 39% and 47% in hypothyroid animals."

Salgado & Mulroy C84,321/59: In rats, the cardiovascular changes produced by DOC following sensitization by uninephrectomy and NaCl are inhibited by hypophysectomy or thyroidectomy, although not all the lesions are blocked to an equal extent.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many among these drugs, and inhibits the protective effect of ethylestrenol.

Fluorocortisol Acetate ← cf. also Tables 12–14

DOC ← cf. also Table 15

Triamcinolone ← cf. also Table 18

Cortisone ← *Thyroxine*: McGuire et al. *E90,938/59, E91,579/59*

Testoids ← cf. also *Selye B40,000/50, p. 631; G60,083/70, p. 401.*

Caridroit & Arvy A57,397/42: In castrate mice, thyroxine increases the seminal vesicle enlargement produced by testosterone.

Selye et al. B229/45: In rats, the renotrophic action of methyltestosterone is greatly enhanced by thyroxine.

Masson 96,171/47: In orchidectomized mice, thyroxine increases the stimulation of the seminal vesicles by testosterone, but the effect is not very marked and may even be reversed depending upon the dose level at which the two hormones are given.

Bradlow et al. C27,897/56: In man, studies with radioactive testosterone suggest that T3 markedly influences the metabolism of this testoid, in that conversion into androsterone is increased with a concomitant fall in etiocholanolone.

Androst-4-ene-3,17-dione ← *Thyroxine*: McGuire et al. *E90,938/59, E91,579/59*

Androst-4-ene-3,17-dione ← *Triiodothyronine*: McGuire et al. *E90,938/59*

Folliculoids ← cf. also *Selye G60,083/70, p. 406.*

Benoit & Clavert B27,669/48: In ducks, estradiol stimulates the proliferation of spongy bone consisting of fine trabeculae. Thyroidectomy retards this bone proliferation whereas conjoint treatment with thyroxine and estradiol leads to abundant development of thick trabeculae.

von Faber C6,925/55: In cockerels, the hypercalcemia produced by stilbestrol is inhibited by concurrent administration of thyroxine.

Common et al. D12,509/61: In immature pullets, the oviduct-stimulating effect of estradiol is greatly increased by the administration of thiouracil p.o.

Kulcsar-Gergely & Kulcsar G71,532/62: In rats, thyroidectomy diminishes, whereas thy-

roid extract increases the hepatotoxicity of CCl_4 . Correspondingly, the sexual cycle is accelerated by thyroidectomy and delayed by thyroid hormone treatment as a result of changes in hepatic folliculoid degradation.

Estradiol ← cf. also *Table 16*

Progesterone ← cf. *Table 17*

Steroidases in General (incl. Bile Acids, Cholesterol) ← cf. also *Cholesterol under Drugs*

Schmidt 27,511/34: In guinea pigs, gastric ulcer formation following i.p. injection of Na-glycocholate or Na-taurocholate is diminished following pretreatment with thyroxine p.o., perhaps because hyperthyroidism causes liver damage and thereby interferes with the biliary excretion of the bile acid.

McGuire Jr. & Tomkins E90,938/59: In rats, thyroxine increases the rate of reduction of Δ^4 -3-ketosteroids by TPNH-dependent microsomal enzymes.

McGuire & Tomkins E91,579/59: In the rat, thyroxine causes a pronounced increase in the microsomal 5α -reductase activity of the liver, but the rate of reduction of some steroid substrates is raised more than that of others. Furthermore, when microsomes are "aged" at 0–5°C for several weeks, the decline in activity varies with different steroid substrates. "Further evidence for the substrate specificity of the 5α hydrogenases was the observation that 4-androstene-3,17-dione strongly inhibited the reduction of cortisone, while the converse was not true." These and other observations suggest that each series of 4-ene-3-ketosteroid hydrogenases, 5α and 5β , contains multiple enzymes capable of discerning small variations in the steroid molecule.

McGuire Jr. & Tomkins D5,722/60: In the microsomal fraction of rat liver, there appear to be at least 5 Δ^4 -3-ketosteroid reductases (5α). When rats are treated with thyroxine, the reductase activity for cortisone, cortisol, DOC, 4-androstene-3,17-dione and 11-deoxy-cortisol (Cpd. S) increases, but the increment is different for each of these substrates.

Danielsson & Tchen G72,327/68 (p. 159): Brief summary of the influence of the thyroid upon cholesterol and bile acid metabolism.

Lehmann & Breuer E8,112/68: The in vitro metabolism of ^{14}C -estrone by the hepatic microsomes of the rat is markedly influenced by in vivo pretreatment with T3 or NaClO_4 . Hyperthyroidism increases, whereas hypothyroidism and severe thyrotoxicosis diminish estrone metabolism.

Lehmann & Breuer H15,110/69: "After incubation of oestrone with the microsomal fractions of liver of euthyroid, hyperthyroid, thyrotoxic as well as hypothyroid rats the following metabolites were identified in the ether soluble fractions: 6 α , 6 β - and 7 α -hydroxy-oestrone, 6 α , 6 β - and 7 α -hydroxy-17 β -oestradiol, 16 α -hydroxyoestrone, oestriol and 17 β -oestradiol. The amounts of metabolites formed depended upon the functional state of the thyroid."

Schweppé & Jungmann H15,266/69: The ability of rat liver microsomes to synthesize cholesterol palmitate, oleate, and linoleate in vitro is increased by the addition of thyroxine or glucagon to the incubation medium. Testosterone increases cholesterol palmitate and oleate formation. 17 β -Estradiol stimulates mainly oleate synthesis.

Schweppé & Jungmann H15,978/69: Observations on the metabolism of marked chole-

terol added together with various hormones to hepatic microsomes of the rat led to the conclusion that "1) cholesterol palmitate and oleate were synthesized most rapidly; 2) at high concentrations, testosterone decreased the formation of all esters but at lower dose levels, testosterone increased the synthesis of cholesterol oleate and palmitate; 3) estradiol caused a two-fold increase in cholesterol oleate formation; 4) ACTH decreased the synthesis rate of cholesterol palmitate and oleate; 5) insulin had a significant inhibitory effect on cholesterol linoleate; 6) epinephrine had little significant effect at the dose level used; and 7) L-thyroxine increased the synthesis of all cholesterol esters."

Pancuronium ← cf. Table 19

Steroids ← Thyroxine: McGuire et al. E90,938/59, D5,722/60

Nonsteroidal Hormones and Hormone-Like Substances ←

Pituitary, Thyroid and Parathyroid Hormones ←. The renotrophic action of crude anterior pituitary extracts is greatly enhanced by thyroxine in the rat.

Several earlier observations suggested that T2, thiourea, and thiouracil interfere with many of the characteristic effects of thyroxine overdosage in rats and mice.

In rats, the activity of thyroxine is greatly augmented after partial hepatectomy. However, it is only when the circulating amount of thyroxine (or T3) is above physiologic limits that the liver plays an important role in its detoxication.

The osteitis fibrosa produced by parathyroid extract in rats is not prevented by thyroidectomy. Apparently, parathyroid hormone does not act through the thyroid as had been claimed by earlier investigators.

On the other hand, pretreatment with thyroxine inhibits the soft tissue calcinosis, osteitis fibrosa, and hypercalcemia produced by parathyroid overdosage in the rat. This inhibition is manifested even after thyroparathyroidectomy, but not after nephrectomy, in contradistinction to calcitonin which inhibits parathyroid extract overdosage even in the absence of the kidneys.

Pancreatic Hormones ←. In rabbits and rats, thyroidectomy decreases resistance to insulin. This effect is much less evident in guinea pigs and dogs. Thyroid feeding has an opposite effect. In cats, thyroidectomy decreases resistance to insulin-induced hypoglycemia even if the parathyroids are preserved.

Thyroidectomy decreases, whereas thyroid extract increases sensitivity to the diabetogenic action of alloxan in rats. The hepatic necrosis produced by alloxan intoxication in rats is prevented by thiouracil, and aggravated by thyroid feeding.

More recent experiments suggest that in mice, sensitivity to insulin convulsions is increased by thyroxine, and that in rats, the diabetogenic effect of alloxan is antagonized by thyroid feeding.

Catecholamines ←. In most species, thyroidectomy increases, whereas thyroid hormones decrease resistance to epinephrine and, to a lesser extent, to norepinephrine. This is true not only of the acute toxicity of catecholamines but also of such chronic changes as the calcifying arteriosclerosis produced in the rabbit.

Histamine and 5-HT ←. In guinea pigs, thyroidectomy protects against otherwise fatal histamine intoxication, whereas thyroxine has an opposite effect. Rats pretreated with thyroxine become extremely sensitive to 5-HT or to anaphylactoidogenic agents which cause histamine and 5-HT liberation from mastocytes.

Thyroxine inhibits the action of 5-HT upon isolated smooth muscles in rats, whereas in the perfused hindquarter, the vasomotor effects of 5-HT are allegedly enhanced by thyroxine.

In man, wheal formation following 5-HT i.c. is reduced in myxedema and increased in thyrotoxicosis.

Hypophyseal Hormones ← cf. also Selye B40,000/50, pp. 515, 552; C92,918/61, p. 40.

Selye et al. B229/45: In rats, the renotrophic action of anterior pituitary extracts is greatly enhanced by thyroxine.

Thyroid Hormones ←

Abelin & Schönenberger 4,290/33: In rats, diiodothyronine inhibits many of the effects of thyroxine overdosage.

Dietrich & Beutner B20,412/44: In mice, thiourea and thiouracil interfere with the action of orally administered thyroid powder when the Reid Hunt test is made the basis of observations. In this test, minute amounts of whole thyroid can be detected by their protective effect against otherwise lethal doses of acetonitrile.

Kellaway et al. B14,515/45: In rats, the activity of thyroxine s.c. was estimated by an increase in pulse rate after partial hepatectomy, thyroidectomy, or bile duct ligation. "It was found (1) that thyroxine activity is greatly intensified in the absence of the liver; (2) that the liver does not play a significant role when the amount of circulating thyroxine is within physiologic limits; (3) that the liver deals with excess hormone by some process of inactivation and not by simple excretion."

**3,3,5-Triido-L-thyronine ← cf. also Table 20
Propylthiouracil ← cf. also Tables 21, 22
Parathyroid Hormone ← cf. also Selye G60,083/70, pp. 401, 413.**

Selye A 36,715/42: In rats, partial hepatectomy, complete thyroidectomy, or bilateral nephrectomy do not prevent the osteitis fibrosa and soft-tissue calcification produced by large doses of parathyroid extract. Apparently, parathyroid hormone does not exert its

action through either the thyroid or the kidney, as had previously been postulated by some investigators. Furthermore, hepatic detoxication does not play an important role in the metabolism of parathyroid hormone.

Côté et al. G46,713/67; Gabbianni et al. G39,934/67; G46,730/68; G46,731/68; Tuchweber et al. G46,759/68: Pretreatment with thyroxine or calcitonin inhibits the soft tissue calcification and osteitis fibrosa induced by parathyroid extract overdosage. In the event of concurrent administration, the effect of the two protective hormones is summated. Thyroxine retains its effect upon calcium metabolism in thyroparathyroidectomized or adrenalectomized but not in nephrectomized rats. The stress of restraint likewise prevents parathyroid overdosage, but the associated biochemical changes are different from those caused by thyroxine.

Pancreatic Hormones ←

Ducheneau 20,846/24: In rabbits, thyroidectomy increases sensitivity to the hypoglycemic and lethal effects of insulin.

Houssay & Busso 20,601/24: In rabbits and rats, thyroidectomy decreases resistance to the toxic effects of insulin. The phenomenon is less evident in guinea pigs and still less in dogs. Thyroid feeding has an opposite effect.

Britton & Myers 18,695/28: In cats, thyroidectomy greatly increases sensitivity to insulin-induced hypoglycemic reactions even if the parathyroids are preserved. However, about 3 weeks after operation, insulin resistance returns to normal and subsequently rises above that level.

Jensen & Grattan 77,887/40: In mice, ACTH, glucocorticoids and cortical extracts increase insulin resistance, whereas other

pituitary hormones and thyroxine have no such effect.

Martinez B15,837/45; *Houssay & Sara* B727/45: In rats, desiccated thyroid feeding increases, whereas thyroidectomy decreases sensitivity to alloxan i.v.

Martinez B2,342/46: In rats, thiouracil diminishes the diabetic action of alloxan and of subtotal pancreatectomy.

Ershoff B24,883/48: In immature female rats fed purified rations containing both pancreas and desiccated thyroid, mortality was high. Similar diets containing only pancreas or desiccated thyroid induced no comparable mortality.

Houssay B60,812/50; *Martinez* B61,239/51: In rats, thyroidectomy or prolonged treatment with thiouracil or cysteine (which increase the free SH groups of tissues) markedly raises resistance to the diabetogenic action of alloxan. These procedures also diminish the incidence of diabetes after subtotal pancreatectomy in the rat, and can even produce permanent cures in a certain percentage of mild diabetic animals.

Martin B88,524/53: In rats, both chloroform and alloxan produce hepatic necrosis and their effect is increased when both agents are given in combination. Thiouracil protects against this form of hepatic necrosis, whereas thyroid feeding aggravates it.

Houssay et al. C15,702/55: In dogs, destruction of the thyroid by ^{131}I alleviates alloxan diabetes.

Hasselblatt & Bastian C59,171/58: In mice sensitivity to insulin convulsions is increased by thyroxine and even more markedly by tolbutamide.

Altieri et al. C71,565/58: In rats, the toxic and diabetogenic effects of alloxan are aggravated by thyroid feeding and inhibited by ^{131}I .

Epinephrine and Norepinephrine ← cf. also *Selye* C92,918/61, pp. 112, 123, 194; G60,083/70, pp. 334, 404.

Busso 26,684/25: In rats, thyroidectomy does not change the resistance to epinephrine or phenol. Morphine appears to be slightly more toxic to thyroidectomized than to intact rats, but the results were irregular.

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine, and atropine but augments sensitivity to pilocarpine and guanidine.

Peltola B57,468/50: In mice, the lethal effect of epinephrine is dose-dependently increased by pretreatment with thyroid powder.

This can serve as a basis for the bioassay of thyroid preparations.

Kroneberg & Hüter B69,838/51: In mice, pretreatment with thyroxine increases mortality to subsequently administered epinephrine, whereas norepinephrine sensitivity is essentially unchanged.

Thibault & Lachaze B69,990/51: In vitro, the effect of epinephrine upon the contraction of the isolated rabbit intestine, spleen and uterus is enhanced by conjoint application of thyroxamine, the "active form of thyroxine."

Kroneberg B87,448/52: In mice, the toxicity of epinephrine, unlike that of norepinephrine, is greatly increased following thyroxine pretreatment.

Brewster Jr. et al. C11,771/56: In dogs, the physiologic changes produced by thyroid extract are abolished following sympathetic blockade. The inotropic, chronotropic and calorigenic effects of epinephrine and norepinephrine are increased by thyroid feeding. "It is concluded that there is a dynamic interrelationship between the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings."

Swanson C22,149/56: In rats, thyroidectomy inhibited while thyroxine potentiated the calorigenic effect of epinephrine.

Osorio C31,059/56: In rats, hypothyroidism (^{131}I , propylthiouracil, thyroidectomy) decreased, whereas hyperthyroidism (desiccated thyroid) increased vascular reactivity to epinephrine, norepinephrine, and angiotensin.

Oester C84,324/59: In rabbits, the arteriosclerosis produced by combined treatment with epinephrine + thyroxine is readily influenced by various conditioning factors.

Hoch D25,881/62: Review (68 pp., 611 refs.) on the biochemical actions of thyroid hormones with a special section on their interactions with epinephrine.

Halpern et al. G67,689/63: In mice, thyroxine greatly increases the toxicity of various sympathomimetic compounds, such as amphetamine, ephedrine, dopa, and dopamine. The toxicity of tyramine and norepinephrine is less markedly enhanced and that of mepipramine is uninfluenced.

Proulx et al. G43,289/66: In rats made hyperthyroid by feeding iodinated casein, "there was a 25% decrease in liver monoamine oxidase and this decrease does not appear to be related to a decrease in body weight. Liver catechol-0-methyl transferase activity was normal in hyperthyroid animals."

Svedmyr G 39,171/66: In rabbits, thyroxine potentiates the calorogenic and hyperlactacidemic effect of epinephrine, leaving its hyperglycemic effect undiminished. Thyroidectomy decreases the calorogenic and hyperlactacidemic actions of epinephrine. The metabolic effects of norepinephrine are less strikingly affected by the thyroid.

Epinephrine ← cf. also Table 23

Histamine and 5-HT ←

Spinelli 14,294/29: In guinea pigs, thyroidectomy protects against otherwise fatal histamine intoxication.

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine, and atropine, but augments sensibility to pilocarpine and guanidine.

Gyermek & Pataky B 65,706/50: In guinea pigs, thyroxine does not influence the bronchoconstriction induced by histamine aerosol.

Sackler et al. B 78,749/53: In rats, thyro-parathyroidectomy increases histamine tolerance, but only in females. Intact rats show no sex difference in histamine tolerance. Gonadectomy raises histamine tolerance in both sexes.

Long C 32,348/57: In guinea pigs, both anaphylactic shock (horse serum) and sensitivity to histamine are greatly increased by pretreatment with thyroxine. Thyroxine also augments the sensitivity of guinea pigs to intradermal tuberculin injection.

Jasmin & Bois C 92,099/60: Rats pretreated with thyroxine become extremely sensitive to 5-HT, and readily die in a state of shock reminiscent of anaphylaxis.

Parratt & West D 235/60: In rats, pretreatment with thyroxine greatly increases sensitivity to dextran, egg white, polymyxin B, compound 48/80, histamine, and 5-HT so that in addition to the anaphylactoid edema, there develops edema and hemorrhage in the intestinal tract. The effect is ascribed to inhibition of intestinal histaminase by thyroxine.

Panisset et al. F 71,775/66: In vitro observations on isolated organs (duodenum, uterus, lung) of rats indicate that thyroxine inhibits the action of 5-HT upon smooth muscle. Conversely, in the perfused hindquarter, the vasomotor effect of 5-HT was enhanced by thyroxine.

Skinohø & Quaade G 72,600/69: In man, wheal formation following intracutaneous injection of 5-HT is reduced in myxedema and increased in thyrotoxicosis. A control study with histamine revealed normal reactivity in myxedema and increased response in thyrotoxicosis.

Angiotensin ←

Osorio C 31,059/56: In rats, hypothyroidism (¹³¹I, propylthiouracil, thyroidectomy) decreased, whereas hyperthyroidism (desiccated thyroid) increased vascular reactivity to epinephrine, norepinephrine, and angiotensin.

Drugs ←

One of the earliest observations on the effect of hormones upon resistance is the great increase in **acetonitrile** tolerance induced by thyroid preparations in the mouse. During the earliest years of the present century this effect was generally used as the basis for the assay of thyroid preparations and even for the determination of thyroid hormone in blood. This so-called "Reid Hunt test" is fairly specific in that other cyanides are not detoxified by thyroid preparations, and other iodine compounds are virtually ineffective in raising acetonitrile resistance. Curiously, in many species such as the rat, thyroid preparations do not protect against acetonitrile and may even decrease resistance to it. Still, even in mice, the specificity of the acetonitrile test is far from absolute, its outcome depending among others, upon the diet, age, and genetic background of the test animals. Hence, the Reid Hunt test is no longer used for bioassay purposes, yet its underlying mechanism continues to be an intriguing problem.

In mice, thyroxine increases the toxicity of **amphetamine** (as it does that of epinephrine and norepinephrine). It has been claimed that this sensitization occurs

especially when the animals are kept under crowded conditions, but the phenomenon is evident even in individually caged mice. T₃ shares this effect of thyroxine. Allegedly, the mortality induced by amphetamine is actually inhibited during the first hour after thyroxine treatment. In rats, thyroidectomy does not significantly affect amphetamine tolerance, but methylthiouracil reduces it, and T₃ aggravates it.

Sensitivity to **anaphylactoidogenic agents** is increased by thyroxine and decreased by thyroidectomy or methylthiouracil treatment in the rat. These observations agree with the similar effects of thyroid hormones upon 5-HT and histamine toxicity as previously discussed.

Numerous investigators dealt with the effect of thyroid hormones upon **barbiturate** intoxication. One of the first observations along these lines was made in cats in which profound phenobarbital anesthesia allegedly inhibits a rise in BMR produced by thyroxine.

In the mouse, the toxic effects of several barbiturates are aggravated, and sleeping time is prolonged by thyroid preparations. The latter also delay the removal of barbiturates from the plasma and tissues of the mouse, whereas thioureas have an inverse effect. However, thyroidectomy allegedly also increases pentobarbital sleeping time.

In rabbits, phenobarbital resistance is said to rise during the first hours following thyroxine administration, whereas the narcotic effect of chloral hydrate is not affected. In rats, thyroidectomy prolongs, while thyroxine shortens pentobarbital anesthesia. It had been claimed at first that these effects are not accompanied by changes in hepatic barbiturate detoxication *in vitro* upon incubation with liver slices. However, more recent observations show that the activity of hexobarbital-metabolizing enzymes in hepatic microsomes is diminished by thyroxine, which would account for the prolongation of anesthesia. It is difficult to see why both thyroidectomy and thyroid preparations prolong barbiturate sleeping time. In fact, some investigators claim that propylthiouracil shortens pentobarbital anesthesia.

Resistance to **carbon monoxide** is diminished by thyroid feeding in rats, presumably because the increased BMR augments oxygen requirements.

According to some investigators, the hepatic cirrhosis produced by **carbon tetrachloride** in the rat is aggravated both by thyroxine and by thiouracil. However, the published results are quite contradictory, presumably because of differences in dosage and timing. Extensive recent investigations suggest that thyroidectomy diminishes, whereas thyroid extract increases the hepatotoxicity of CCl₄; particularly good protection against hepatic cirrhosis is obtained in rats simultaneously thyroidectomized and ovariectomized.

The influence of the thyroid upon the actions of **carcinogens** has also been extensively investigated. The production of cystic and neoplastic hepatic lesions by 2-acetaminofluorene in rats is inhibited by thiouracil; concurrent treatment with thyroid powder and testosterone sensitizes for this carcinogen. Prostatic carcinogenesis induced by topical application of 20-methylcholanthrene is said to be inhibited by T₃ without being affected by methylthiouracil.

The anesthetic effect of **chloral hydrate** is not conspicuously affected by thyroid preparations in the mouse, rat or rabbit.

The toxicity of **chlordiazepoxide** is increased by a thyroid extract or T₃ in the mouse, whereas methylthiouracil appears to have an opposite effect.

The hepatotoxicity of **chloroform** is increased by a thyroid extract and diminished by thiouracil in rats and rabbits.

In rabbits, **cholesterol** atheromatosis and the associated xanthomatous lesions in the liver are inhibited by thyroxine and increased by thyroidectomy or thiouracil treatment. In chicks, various thyroid preparations diminish the hypercholesterolemia, but do not significantly suppress the coronary or aortic atherogenesis. In rats fed a high-fat, high-cholesterol diet, the increase in hepatic and plasma cholesterol is not significantly changed by thyroxine. However, both D- and L-T₃ diminish the changes in plasma lipids while aggravating the hepatic lesions.

The pyrogenic effect of **cocaine** is increased to fatal levels in rabbits pretreated with thyroxine. In rats, thyroxine also aggravates cocaine intoxication.

In view of the excellent protection offered by thyroid preparations against acetonitrile in the mouse, the effects upon other **cyano-compounds** have also been investigated, but sensitivity to these is not strikingly affected by the thyroid.

Since **digitalis** compounds are extensively used in studies on protective steroids, it is of interest that thyroid preparations augment the hemodynamic effects of digitalin in the rabbit, and aggravate the cardiac lesions produced by digitalis alkaloids in cats. Sensitization to digitalis, and particularly to digitoxin, has been observed in various species using different indicators of activity. It is also noteworthy that therapeutic doses of cardiac glycosides allegedly prevent the thyroxine-induced weight loss in the guinea pig. The convulsions and mortality induced by digitoxin overdosage in the rat are not prevented by thyroidectomy or propylthiouracil, nor do these agents inhibit the antidigitoxin activity of PCN. Apparently, the mild goitrogenic effect of the latter is not involved in its protective action against digitoxin.

The toxicity of **ephedrine** (like that of amphetamine, epinephrine and norepinephrine) is increased by thyroxine, not only in "aggregated" mice as claimed previously, but also in separately caged animals.

The toxicity of **imipramine** is increased by thyroxine or T₃, and decreased by thiourea in the mouse.

The catatoxic effect of ethylestrenol against **indomethacin**-induced intestinal ulceration and mortality is inhibited by thyroxine in the rat. Given by itself, thyroxine shortens survival after indomethacin intoxication.

The skeletal changes produced by **lathyrogens** in the rat are most actively prevented by various thyroid preparations and aggravated by thyroidectomy or thiouracil. Neurolathyrism produced by IDPN and other neurolathyrogens are similarly influenced, but angiolathyrism is not significantly affected by thyroid hormones. T₃ is about 50 times as potent as thyroxine in preventing osteolathyrism. Since both L- and D-T₃ suppress osteolathyrism in the rat, the effect is allegedly independent of the classical thyroid hormone actions.

The nephrocalcinosis characteristic of **magnesium** deficiency is prevented by thyroxine in the rat, but allegedly some manifestations of the Mg-deprivation are also inhibited by thyroparathyroidectomy.

Meprobamate intoxication is counteracted by catatoxic steroids but aggravated by thyroxine; in the case of concurrent administration of the two types of hormones, they mutually tend to antagonize each other's influence in this respect.

Morphine resistance is diminished in mice, rats, and guinea pigs by pretreatment with thyroid extracts. Thyroidectomy does not appear to have a consistent effect

upon morphine intoxication or upon the development of morphine withdrawal symptoms. However, in most of these respects, the published data are contradictory.

The fatal pulmonary edema produced by ozone inhalation in mice and rats is prevented by thiourea and aggravated by thyroxine or T3. Thyroxine and T3 increase the sensitivity of the mouse and rat to the induction of convulsions by pentylenetetrazol. The influence of thyroidectomy and thiouracil is less clear-cut.

Thyroxine increases the toxicity of several pesticides and antagonizes the protective action of catatonic steroids. However, this effect of the thyroid hormone is rarely very pronounced, and often absent.

The nephrocalcinosis produced in rats by dietary excess of certain phosphates is inhibited both by thyroparathyroidectomy and by thyroxine in the rat. However, allegedly, propylthiouracil increases this type of nephrocalcinosis.

Physostigmine intoxication is aggravated by thyroxine in the rat.

Picrotoxin poisoning is inhibited by thyroidectomy in guinea pigs. In rats, thyroxine aggravates picrotoxin poisoning and counteracts the protective effect of ethylestrenol.

In mice and rats, thyroid preparations increase the toxicity of reserpine.

The characteristic syndrome of tyrosine intoxication (keratitis, conjunctivitis, alopecia, inflammation of the paws and snout) produced under certain conditions in young rats is inhibited by thiouracil and aggravated by thyroxine.

There undoubtedly exist close interrelations between the thyroid and **vitamin-A** metabolism. Earlier observations suggested that the toxicity of thyroxine is partly inhibited by carotene (the precursor of vitamin A) in the rat. Furthermore, in goats, the milk is normally rich in vitamin A, but virtually free of carotene, whereas the reverse is true after thyroidectomy. In guinea pigs, thyroxine inhibits the hepatic storage of carotene and its transformation into vitamin A. Early investigators claimed that hypervitaminosis A can be prevented by thyroxine in the rat, but subsequent experiments failed to confirm this. The pertinent literature is very confusing. In rats kept on a vitamin-A deficient diet, thiourea blocks the protective effect of carotene, and this blockade can be in turn abolished by thyroid powder. Yet, it was claimed that thiouracil prolongs the survival of the rat on a vitamin-A deficient diet.

In rats, the hepatic storage of vitamin A is increased by thyroxine, but the total vitamin-A storage of the body is unaffected. Both L- and D-T3 aggravate hypervitaminosis A in the rat. The offspring of rats given excessive amounts of vitamin A during pregnancy often show deformities of the skull and brain, which are aggravated by methylthiouracil treatment of the pregnant mother.

In pigeons kept on **vitamin-B** deficient polished rice, wasting and death were accelerated by thyroid feeding, but this may not have been true beriberi. In vitamin-B complex deficient rats, thyroid feeding aggravates the resulting skeletal lesions. On the other hand, survival on a thiamine deficient diet is prolonged in thyroparathyroidectomized rats, but not significantly altered by desiccated thyroid. Conversely, thiamine antagonizes thyroxine overdosage in the rat.

Vitamin-B₁₂ requirements are greatly augmented by thyroxine in the rat, and although vitamin-B₁₂ possesses no lipotropic potency itself, it prevents the hepatic steatosis produced in thyroxine-treated rats by hypolipotropic diets.

In guinea pigs fed **vitamin-C** deficient diets, the development of scurvy is accelerated by thyroid feeding. Thyroidectomy also aggravates the scorbutic lesions but does not accelerate their onset.

The development of bone lesions on **vitamin-D** deficient diets is not very consistently influenced by thyroidectomy or thyroid administration in the rat. However, the calcinosis produced by excess of vitamin D or DHT is aggravated by thyroxine in the rat. Curiously in rabbits, the calcinosis and other manifestations of **vitamin-D₂** overdosage are accentuated by methylthiouracil, whereas in the cow, the production of calcinosis by **vitamin-D₃** overdosage has been said to be prevented by thyroxine.

In the chick, **vitamin-E** requirements are increased by thyroid preparations and decreased by thiourea. In rats, the muscular dystrophy produced by **vitamin-E** deficiency is aggravated by thyroid feeding. In rabbits, suppression of thyroid activity by radioiodine exerts a certain prophylactic effect.

Zoxazolamine paralysis is aggravated by thyroidectomy and inhibited by thyroxine or T3 in the rat owing to changes in hepatic microsomal zoxazolamine metabolism.

Acetaldehyde ←

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites, pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

2-Acetaminofluorene ← cf. **Carcinogens** (AAF)

Acetanilide ← cf. *Table 24*

Acetonitrile ←

GUINEA PIG

Spinelli 10,086/31: In guinea pigs thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine, and atropine, but augments sensitivity to pilocarpine and guanidine.

MOUSE

Hunt 60,064/05: In mice, thyroid feeding greatly increases resistance to acetonitrile but not to various other cyanides, such as hydrocyanic acid or sodium ferricyanide.

Hunt 49,717/07: In mice, acetonitrile resistance is increased by injections of the blood of hyperthyroid patients.

Hunt & Seidell 46,617/10: In mice, the protective effect of thyroid extract against acetonitrile is due to the hormone itself and

not to iodine. Other iodine preparations do not have a protective action. Unlike mice, rats are actually sensitized to acetonitrile by thyroid pretreatment.

Hunt 49,718/11: In mice, the resistance to acetonitrile induced by thyroid extract is subject to considerable variation depending upon the diet.

Wuth A 48,026/21: In mice, tyramine and diiodotyramine, like thyroid extract, offer protection against acetonitrile whereas histamine does not.

Miura 13,081/22: Mice are protected against acetonitrile by thyroxine and desiccated thyroid, but not by KI or T2.

Hunt 13,889/23: Pretreatment with thyroid preparations greatly increases the resistance of mice to acetonitrile, whereas the reverse is true in many other species.

Gellhorn 16,839/23: In mice, resistance against acetonitrile can be increased not only by thyroid extract, but to a lesser extent also by extracts of various other tissues. These preparations also augment resistance to KCN and propionitrile, whereas thyroidectomy and orchidectomy have an opposite effect.

von Zwehl 25,477/26: Female mice pretreated with repeated doses of T2 tolerate 2–3 lethal doses of acetonitrile, whereas in males, a significant protective effect could not be demonstrated.

Paal 22,603/30: Review of the literature, and extensive personal studies on acetonitrile test in mice, and its use for the determination of thyroid hormone in human blood. Thyroidectomy does not increase the resistance of

mice to acetonitrile, but diminishes the protective effect of thyroxine. Concurrent treatment with insulin also inhibits the prevention of acetonitrile toxicity by thyroxine.

Knaab 14,828/33: Discussion of the earlier literature, and personal observations on factors influencing the effect of thyroxine upon acetonitrile resistance in the mouse.

Montgomery 18,184/33: Review of the literature on the acetonitrile test for thyroid preparations in mice. The protective effect of thyroid is confirmed, but individual variations and dietary factors alter responsiveness so much that the technique is unsuited for bioassay purposes.

Grab 44,536/33: In mice, about 50 µg of thyroxine suffices to protect with certainty against otherwise lethal acetonitrile intoxication.

Paal 18,183/33: In mice, exposure to light greatly influences sensitivity to acetonitrile. Even after thyroidectomy, daylight as well as ultraviolet irradiation increase the MLD of acetonitrile. Hence, resistance to this drug is not always influenced through variations in thyroid activity.

Santo 27,439/34: Review on the factors influencing the Reid Hunt-reaction in mice.

Fellinger & Hochstädt 63,744/35: In mice, the protection against acetonitrile offered by thyroxine or TTH is blocked by an extract of blood that contains the "ether soluble anti-thyroid substances."

Fleischmann & Kann 67,360/36: In mice, vitamin A antagonizes the protective effect of thyroxine against acetonitrile intoxication. Vitamin A also antagonizes the effect of thyroxine upon tadpole metamorphosis.

Dietrich & Beutner B20,412/44: In mice, thiourea and thiouracil interfere with the action of orally administered thyroid powder when the Reid Hunt test is made the basis of observations. In this test, minute amounts of whole thyroid can be detected by their protective effect against otherwise lethal doses of acetonitrile.

VARIA

Hunt 49,716/07: Comparative studies on the effect of thyroid extract upon the acetonitrile and morphine resistance of mice, rats, and guinea pigs.

Hunt & Seidell 50,346/09: Monograph (115 pp.) on the use of the acetonitrile test for thyroid function. In rats, thyroid feeding actually lowers resistance to acetonitrile.

Hunt 50,349/10: Very detailed description of the acetonitrile test for thyroid. Here, special attention is placed upon the modifying influence of the diet, seasonal variations, species, and other conditioning factors.

Oehme & Paal 62,442/32: Review (42 pp., about 200 refs.) on the technique and clinical applications of the acetonitrile test for thyroid action, with a survey of the numerous factors that can influence its outcome.

Aconitine ←

Spinelli 10,086/31: In guinea pigs thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine, and atropine, but augments sensitivity to pilocarpine and guanidine.

Acrylamide ← cf. Table 25

Acrylonitrile ← cf. Table 26

Adenosine Diphosphate ←

Chandler & Nordöy G22,017/64: In rats, the pulmonary thrombi produced by ADP i.v. are stabilized by pretreatment with propylthiouracil, perhaps because the inactivation of ADP is delayed.

Allyl Alcohol ←

Srinivasan et al. G78,977/70: In rats, pretreatment with thyroxine aggravates the hepatic damage produced by allyl alcohol (judged by hepatic histology, serum GPT and BSP).

Allylformiate ←

Spiess-Bertschinger B40,585/44: In rats, the hepatic lesions produced by allylformiate are aggravated by thyroid feeding, but regenerative phenomena are active. After thyroidectomy, the hepatic lesions are particularly severe and characterized by necrosis without regeneration.

o-Aminophenol ← 6-Propylthiouracil,
Mouse: Werder et al. G12,065/64

Aminopyrine ← cf. Table 27

Aminopyrine ← Thyroxine: Kato et al. F57,817/65

Aminopyrine ← Thyroidectomy:
Orrenius et al. G66,249/65

p-Aminosalicylate ←

Mehrotra & Sarna D14,287/61: In rats, the hepatic lesions and glycogen infiltration

produced by p-aminosalicylate (PAS) were not prevented by thyroxine. Hence, these changes are not due to hypothyroidism.

Amphetamine ←

MOUSE

Pfeifer et al. D12,952/60: In mice, the increased motility induced by amphetamine is inhibited during the first hour after thyroxine treatment. The possible biochemical reasons for this "negative tendency" during the early phase of thyroxine action are described.

Askew G72,695/62; Halpern et al. G11,305/63: In mice, thyroxine increases the lethal effect of amphetamine.

Halpern et al. G63,588/63: In mice, thyroxine pretreatment diminishes resistance to amphetamine and DL-dopa, especially under conditions of crowding.

Gayet-Hallion & Bouvet F16,484/64: In mice kept under crowded conditions, the toxicity of amphetamine is diminished by pretreatment with the blood of thyroidectomized horses.

Halpern et al. F24,137/64: In mice, the toxicity of amphetamine and ephedrine is increased by pretreatment with thyroxine not only—as had been previously shown—when several animals are kept together in a jar, but also when they are kept in solitary cages.

Moore F36,358/65: In mice, the toxicity of d-amphetamines is greatly augmented by pretreatment with T3. Simultaneously, there develops a dose-dependent reduction in the levels of brain, heart, and spleen norepinephrine, liver glycogen and blood glucose. Similar changes are observed if amphetamine is given to mice crowded ("aggregated") in small cages.

Moore G36,616/65: In mice, pretreatment with T3 greatly increases sensitivity to the lethal effect of amphetamine. "Chlorpromazine, phenoxybenzamine, and propranolol pretreatment reduced the lethality of d-amphetamine in hyperthyroid mice while α -methyl-m-tyrosine, α -methyl-p-tyrosine, and reserpine pretreatment did not. The toxicity of α -methyl-m-tyrosine was enhanced in hyperthyroid mice."

Winter G71,836/65: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazol is increased by T3 or thyroid powder, whereas the narcotic effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects. [The experimental conditions are not

described in sufficient detail to evaluate these findings (H.S.).]

Winter F64,465/66; F98,019/68: In mice, pretreatment with thyroid extract p.o. increases the toxicity of reserpine, chlordiazepoxide, imipramine, and amphetamine.

RAT

Tormey & Lasagna C80,689/60: In rats, thyroidectomy does not significantly affect tolerance to amphetamine.

Mantegazza & Riva F47,703/65: In rats, methylthiouracil reduces various manifestations of amphetamine intoxication.

Dolfini & Kobayashi F91,611/67: In rats, amphetamine causes more pronounced hyperthermia after pretreatment with T3 than following thyroidectomy or thiouracil treatment.

Mantegazza et al. H7,676/68: In rats, pretreatment with methylthiouracil reduces the toxicity, hyperthermia, hyperglycemia, and the increase in plasma free fatty acids induced by amphetamine more than the increased spontaneous activity and anorexia. This dissociation of effects might reflect an altered metabolic pattern of amphetamine.

Amyl Nitrate ←

Specht 13,475/23: In guinea pigs, neither thyroidectomy nor orchidectomy influences the course of the convulsions produced by amyl nitrate inhalation or electric irritation of peripheral nerves.

Anaphylactoid Edema ← cf. also Selye G46,715/68, pp. 117, 180, 184, 199.

Parratt & West D235/60: In rats, pretreatment with thyroxine greatly increases sensitivity to dextran, egg-white, polymyxin B, compound 48/80, histamine, and 5-HT so that in addition to the anaphylactoid edema, there develops edema and hemorrhage in the intestinal tract. The effect is ascribed to inhibition of intestinal histaminase by thyroxine.

Spencer & West D32,617/62: In rats, the anaphylactoid edema produced by dextran or egg-white is diminished by thyroidectomy or methylthiouracil, and increased by thyroxine or T3.

Aniline ← Thyroxine + Orchidectomy + Methyltestosterone: Kato et al. F57,817/65

Anticoagulants ←

Lowenthal & Fisher C40,044/57: In rats, the anticoagulant effect of warfarin is increased by thyroxine and diminished by hypothyroidism (methimazole treatment).

Owens et al. D21,725/62: In man, dextrothyroxine potentiates the anticoagulant action of warfarin.

Solomon & Schrogie H1,868/68: In women, thyroxine greatly potentiates the anticoagulant effect of warfarin. Analysis of the data (according to the method of Lineweaver and Burk) suggests that an increased affinity of the drug for its receptor site is responsible for the potentiation of its effect. The literature on the increase in the response to various indirect anticoagulants by thyroxine in man is briefly reviewed.

Selye G60,094/70: In rats, the fatal hemorrhagic diathesis produced by phenindione is inhibited by ethylestrenol, CS-1, spironolactone, norbolethone, and oxandrolone. Progesterone, hydroxydione, DOC, and estradiol have a much less pronounced effect. Prednisolone, triamcinolone, and thyroxine are inactive.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate, and picrotoxin. Thyroxine increases the toxicity of many among these drugs and inhibits the protective effect of ethylestrenol.

Bishydroxycoumarin ← cf. also Table 28

Phenindione ← cf. also Table 29

Antimony ←

Shih-Chi et al. C72,194/58: In mice, thyroxine decreases, whereas propylthiouracil increases resistance to the fatal effect of intoxication with ammonium antimonyl gluconate i.p. The differences are not explicable on the basis of the distribution or excretion of antimony.

Arsenic ←

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract does not influence resistance to sodium arsenite.

Bogdanovitch & Varagitch G71,534/54; Bogdanovitch C18,912/56: In rats, pretreatment with thyroid extract increases, whereas methylthiouracil decreases the toxicity of organic

arsenicals such as oxophenarsine or dichlorophenarsine.

Atropine ←

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract does not change resistance to atropine.

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine, and atropine, but augments sensitivity to pilocarpine and guanidine.

Barbiturates ←**CAT**

von Issekutz & von Issekutz Jr. 45,261/35: In cats, profound phenobarbital anesthesia inhibits the rise in BMR normally produced by thyroxine. It is assumed that thyroxine raises oxygen consumption indirectly through an effect upon the higher nervous centers.

FROG

Richards 79,646/41: In the frog, stimulation of metabolism by thyroxine increases susceptibility to pentobarbital.

MOUSE

Prange Jr. & Lipton F56,756/65: In mice, the toxic effects of the convulsant barbiturate 5-(1,3-dimethylbutyl)-5-ethyl barbituric acid (DMBEB) are aggravated by desiccated thyroid p.o., and diminished by propylthiouracil.

Winter G71,836/65: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazol is increased by T3 or thyroid powder, whereas the narcotic effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects. [The experimental conditions are not described in sufficient detail to evaluate these findings (H.S.).]

Schrogie & Solomon C43,019/66: In mice, the metabolism of bishydroxycoumarin was markedly inhibited by both L-and D-thyroxine. The demethylation of meperidine was likewise inhibited by both isomers but particularly by D-thyroxine. L-thyroxine also increased the lethal effect of meperidine overdosage. Pentobarbital sleeping time was prolonged in mice treated with either L- or D-thyroxine, but the latter was more active in this respect.

Ellinwood F64,417/66: In mice, dichloroisoproterenol (a β -adrenergic blocker) does not influence pentobarbital sleeping time and, far

from inhibiting, actually potentiates the prolongation of anesthesia by thyroid feeding. It is unlikely therefore that thyroid would increase barbiturate hypnosis through the production of epinephrine.

Klinger F66,416/66: In mice and rats, large doses of thyroxine prolong hexobarbital sleeping time and diminish the resistance induced by barbital pretreatment. The associated changes in ascorbic acid metabolism are discussed.

Prange et al. G40,154/66: In mice, thyroid feeding increases sensitivity to various barbiturates and delays their removal from the brain, liver, and plasma. Propylthiouracil has an inverse effect. In rats, thyroxine slightly and thyroidectomy markedly increase pentobarbital sleeping time.

Spencer and Waite H30,100/70: In mice, pretreatment with thyroxine enhances the hypnotic effect of very small doses of thiopental. Earlier experimenters had shown that hyperthyroidism increases sensitivity to larger doses of barbiturates, but in the present case, metabolic studies suggest that an "enhanced rate of redistribution of thiopentone brought about by increased peripheral and cerebral blood flow in hyperthyroid mice" was probably responsible for the diminished anesthetic effect.

Hexobarbital ← Thiouracil, Mouse: Wenzel et al. G76,357/55*

Hexobarbital ← Triiodothyronine, Mouse: Holtz et al. C76,300/58*

Pentobarbital, Thiopental ← Thyroid extract, Mouse: Ellinwood et al. E39,187/64*; Prange et al. G40,154/66*

RABBIT

Zárday & Weiner: 53,715/35: In rabbits, thyroxine s.c. does not influence the narcotic effect of chloral hydrate given a few hours later. On the other hand, the resistance to phenobarbital rises through the influence of thyroxine under similar conditions.

RAT

Scarborough 34,971/36: In rats, feeding of thyroid extract diminishes the anesthetic effect of pentobarbital.

Horinaga A36,414/41: Thyroidectomy increases barbiturate sensitivity in the rat.

Robillard et al. B66,661/51: In rats, thyroidectomy prolongs pentobarbital anesthesia and delays hepatic detoxication of the drug, whereas thyroxine pretreatment diminishes the duration and depth of this anesthesia with-

out enhancing the hepatic detoxication of pentobarbital as determined by incubation of the drug with liver slices. After simultaneous thyroidectomy and orchidectomy, pentobarbital detoxication is more markedly delayed than after simple thyroidectomy or orchidectomy, and the anesthetic effect is correspondingly further intensified than after ablation of the thyroid or testes alone.

Holck et al. B95,270/54: In rats, thyroidectomy or propylthiouracil treatment increased the recovery time from isopropyl- β -bromallyl barbituric acid, propallylonal (Nostal), thiopental, and hexobarbital. Thyroglobulin or thyroxine caused no consistent shortening of the average recovery time from isopropyl- β -bromallyl barbituric acid; propallylonal (Nostal). Either of these effects is also largely influenced by the sex of the animals.

Robillard et al. G67,325/54: Thyroidectomy prolongs pentobarbital anesthesia in intact, and even much more in castrate adult male rats. Thyroxine decreases the anesthetic effect of pentobarbital in thyroidectomized rats even below the normal level. Liver homogenates of thyroidectomized rats metabolize pentobarbital in vitro less rapidly than those of normal rats, but pretreatment in vivo with thyroxine does not increase the pentobarbital-metabolizing activity of these homogenates above the control value.

Lanzetta C68,990/58: In rats, thyroxine or dinitrophenol given i.p. 30 min before thiopental prolongs the anesthetic effect of the latter, presumably through uncoupling of oxidative phosphorylation.

Conney & Garren D93,666/61: In the rat, thyroxine prolongs the duration of hexobarbital anesthesia by decreasing the activity of hexobarbital-metabolizing enzymes in hepatic microsomes.

Kato & Gillette F57,817/65: The metabolism of aminopyrine and hexobarbital by hepatic microsomes of male rats is impaired by adrenalectomy, castration, hypoxia, ACTH, formaldehyde, epinephrine, morphine, alloxan, or thyroxine. The metabolism of aniline and zoxazolamine is not appreciably decreased by any of these agents; in fact, the hydroxylation of aniline is enhanced by thyroxine or alloxan. Apparently, the treatments impair mainly the sex-dependent enzymes. Accordingly, the corresponding enzymic functions of the hepatic microsomes of female rats are not significantly impaired by the agents which do have an inhibitory effect in males.

Kato & Takahashi G55,715/68: Thyroxine decreased the N-demethylation of aminopyrine and hydroxylation of hexobarbital by liver microsomes of male rats. By contrast, thyroxine increased the metabolism of aminopyrine and hexobarbital in females. The hydroxylation of aniline and reduction of p-nitrobenzoic acid were increased in both sexes. The effect of thyroxine and thyroidectomy upon other microsomal enzyme systems has also been examined.

Harbison & Becker H10,917/69: Thyroidectomy greatly prolonged hexobarbital sleeping time and zoxazolamine paralysis in rats. T3 increased the response to hexobarbital but diminished the effect of zoxazolamine. The mortality rates induced by high doses of hexobarbital, thiopental, amobarbital, pentobarbital, and phenobarbital were all significantly increased in rats pretreated with T3.

Kato et al. H11,854/69: "The administration of thyroxine or starvation resulted in marked decrease in the hydroxylation of pentobarbital and hexobarbital and N-demethylation of aminopyrine in male rats, whereas the hydroxylation of aniline and zoxazolamine and N-demethylation of N-methylaniline were significantly increased."

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate, and picrotoxin. Thyroxine increases the toxicity of many among these drugs and inhibits the protective effect of ethylestrenol.

Barbiturates ← cf. also Tables 30—34

VARIA

Glaubach & Pick 11,431/30: In guinea pigs and rabbits, the hypothermia produced by phenobarbital is counteracted by thyroxine pretreatment.

Zárday & Weiner A52,879/34: Anesthesia with morphine in rats, and with chloral hydrate in rabbits was not significantly influenced by pretreatment with thyroxine s.c., one hour before the anesthetics. On the other hand, phenobarbital anesthesia was prolonged by thyroxine pretreatment in rabbits under identical conditions. Similar observations have been made on patients suffering from thyrotoxicosis, in that they are unusually resistant to barbiturates but not to other anesthetics. This selective antagonism is ascribed to interactions

between thyroxine and barbiturates at some common receptor site in the midbrain.

Ellinwood Jr. & Prange Jr. E39,187/64: Review of earlier observations on the effect of thyroid and thiourea preparations upon pentobarbital sleeping time in mice and rats. Since thyroid hormones and epinephrine are synergistic in many respects, mice were treated with various combinations of these agents. Pentobarbital anesthesia was prolonged by desiccated thyroid and shortened by propylthiouracil pretreatment. High doses of epinephrine prolonged sleeping time in themselves and potentiated the effect of thyroid feeding. The prolongation of pentobarbital sleeping time by epinephrine may be due to depletion of hepatic glycogen which interferes with hepatic microsomal drug metabolism.

Barbital ← **Thyroidectomy:** Boyland et al. D47,605/62*

Hexobarbital ← **Thyroxine:** Conney et al. D93,666/61*

Pentobarbital ← **Thyroidectomy + Thyroxine:** Robillard et al. G67,325/54*; Prange et al. G40,154/66*

Bilirubin ← **Triiodothyronine + Age, Man:** Lees et al. C74,543/59*

Cadmium ← cf. Table 35

Caffeine ←

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract did not change resistance to caffeine.

Strubelt et al. G78,572/70: In rats, T3 increases, whereas thyroidectomy decreases, the calorogenic response to theophylline and caffeine, probably because the thyroid hormone activates adenyl cyclase and/or inhibits phosphodiesterase.

Caramiphen ← cf. Table 36

Carbon Dioxide ←

Barbour & Seevers 84,296/43: In rats, exposure to cold and an excess of CO₂ produces a state of narcosis against which considerable resistance can be induced by thyroid extract. No such effect was obtained by dinitrophenol.

Carbon Monoxide ←

Mack & Smith 45,162/34: In rats, both thyroid feeding and dinitrophenol shorten survival during CO poisoning.

Smith et al. 45,163/35: Male rats are more sensitive to the lethal action of illuminating

gas than females. This difference is eliminated by gonadectomy. Thyroid feeding or dinitrophenol injections decrease survival time.

Carbon Tetrachloride ←

Lesca & Mosca B48,329/49: In rats, the hepatic cirrhosis produced by CCl_4 is aggravated both by thiouracil and by thyroxine. However, survival time is increased in the thyroxine-treated rat.

Aragona & Barone B92,455/53: In rats, thyroxine protects the liver against the damaging effect of CCl_4 .

Calvert & Brody C82,829/60: In rats, brief pretreatment with thyroxine increases, whereas previous thyroidectomy diminishes the metabolic changes produced by CCl_4 intoxication. Adrenal catecholamines are strongly reduced in hyperthyroid and only slightly reduced in hypothyroid animals. "The changes are consistent with a concept of anoxia being the primary event in CCl_4 hepatotoxicity."

Calvert & Brody D61,412/61: Thyroxine pretreatment increases the susceptibility of the rat to the hepatotoxicity of CCl_4 .

Kulcsár-Gergely & Kulcsár G71,532/62; E33,917/63: In rats, thyroidectomy diminishes, whereas thyroid extract increases the hepatotoxicity of CCl_4 . Correspondingly, the sexual cycle is accelerated by thyroidectomy and delayed by thyroid hormone treatment as a result of changes in hepatic folliculoid degradation.

Kulcsár-Gergely et al. F32,037/64: In rats, simultaneous thyroidectomy and ovariectomy offer some protection against the induction of hepatic cirrhosis by CCl_4 .

Kulcsár-Gergely & Kulcsár G1,372/64: In rats intoxicated with CCl_4 , survival is increased by ovariectomy and thyroidectomy.

Berenesi et al. G33,802/65: In rats, the production of hepatic lesions by CCl_4 is diminished after thyroidectomy or methylthiouracil treatment.

Berencsi & Krompecher G43,712/66: In rats, the hepatic damage caused by CCl_4 is decreased by thyroidectomy or methylthiouracil and increased by thyroxine or T₃.

Kulcsár & Kulcsár-Gergely F74,930/66: In rats, ovariectomy, thyroidectomy, or removal of both glands, offers partial protection against CCl_4 intoxication.

Srinivasan & Balwani G64,503/68: In rats, pretreatment with thyroxine increased the liver damage produced by subsequent administration of CCl_4 or thioacetamide.

Kulcsár et al. H14,649/69: In rats, thyroidectomy offers some protection against the production of hepatic damage by CCl_4 ; this may be due to altered mucopolysaccharide formation.

Kulcsár et al. H24,478/70: In rats, thyroxine increases, whereas thyroidectomy decreases, the hepatotoxicity of CCl_4 as judged by BSP elimination.

Carcinogens ←

Cantarow et al. B18,774/46: In rats given 2-acetaminofluorene p.o., the development of cystic and neoplastic hepatic lesions was accelerated and intensified by GTH (pregnant mare serum), estradiol, and testosterone, but inhibited by thiouracil. "This phenomenon may be related to the role of the liver in the intermediary metabolism and excretion of the sex steroid." In the hyperplastic target organs of the sex hormones, tumors did not occur, in contrast to the high incidence of tumors in the thyroids of rats given thiouracil simultaneously with the carcinogens.

Miller Jr. & Baumann G74,552/51: Rats made hyperthyroid by feeding iodinated casein + p-dimethylaminoazobenzene (DAB), exhibited a high mortality, and the incidence of tumors in the survivors was very great. Thiouracil and propylthiouracil did not alter tumor incidence remarkably. "Liver slices from hyperthyroid rats destroyed less than one-fourth as much DAB as slices from normal rats."

Bielschowsky & Hall C194/53: In rats, the production of hepatomas by AF orAAF is inhibited following thyroidectomy. The protection is manifest only if the thyroid is removed before the administration of the carcinogens and even then it is restricted to the liver. The production by AF or AAF of extrahepatic neoplasms is not prevented.

Reid B93,930/54: Review (18 pp., 181 refs.) on the effect of STH and corticoids upon carcinogen-induced and transplantable neoplasms.

Klärner & Klärner C45,812/58: In BAF₁ mice, the growth of urethan-induced pulmonary tumors is significantly inhibited by alloxan diabetes and exposure to heat, but only slightly affected by thyroxine and insulin.

Bielschowsky D10,255/61: In rats, hypophysectomy, thyroidectomy and adrenalectomy inhibit the development of hepatomas by treatment with 2-acetylaminofluorene (AAF) or 2-aminofluorene (AF).

Leathem & Oddis D2,742/61: Female rats are less responsive than males to the induction of hepatomas by AAF. Thyroid feeding increases the incidence of hepatomas in females treated with AAF. It has the same effect in mice of both sexes given DMBA.

Sherwin-Weidenreich & Herrmann D67,842/63: In mice, tumor induction by DMBA is not inhibited, and perhaps even accelerated, by T3.

Sterental et al. D61,608/63: In rats, mammary tumors induced by DMBA regressed after adrenalectomy + ovariectomy or hypophysectomy. Folliculoid treatment reactivated tumor growth after adrenalectomy + ovariectomy but not after hypophysectomy. These tumors remained unresponsive to folliculoids after hypophysectomy even if thyroid and cortisone replacement therapy was given.

Reuber F4,431/64: In rats, the production of hepatomas by N-2-fluorenyldiacetamide was prevented by orchidectomy or thyroidectomy. However, the carcinogenic effect was restored in thyroidectomized animals by thyroid feeding.

Weidenreich-Sherwin & Herrmann F16,179/64: In mice, the production of skin tumors by topical application of 3-MC is considerably enhanced by T3.

Reuber F36,234/65: Concurrent treatment with testosterone and thyroid powder sensitizes the rat for the production of hepatic cirrhosis and hepatomas by N-2-fluorenyldiacetamide.

Goodall F71,302/66: In rats, the induction of hepatic tumors by 2-aminofluorene is inhibited by thyroidectomy.

Ronzoni et al. H18,409/68: In rats, prostatic carcinogenesis induced by the introduction of 20-methylcholanthrene crystals into the prostate is inhibited by ACTH, triiodothyronine and, to a lesser extent, by progesterone and 19-nortestosterone phenylpropionate. Estradiol and cortisone facilitate carcinogenesis, whereas testosterone, orchidectomy, and methylthiouracil failed to influence it.

Davidson et al. H10,206/69: In rats made hypothyroid by ^{131}I , the incidence of mammary cancer induction by DMBA is increased. Hypothyroidism induced by iodine deficiency did not share this effect and radio-iodine may have acted by radiation injury to the breast tissue rather than the associated hypothyroidism.

3-MC ← Thyroidectomy: Boyland et al. D47,605/62*

Carisoprodol ← cf. Table 37

***Carotene* ← cf. Vitamin A**

***Choline* ←**

Tabachnick et al. C50,317/58: In mice, thyroxine increases sensitivity to decamethonium and neostigmine but not to D-tubocurarine or succinylcholine. Rabbits pretreated with thyroxine also become more sensitive to decamethonium. It is tentatively suggested that the motor disturbances associated with hyperthyroidism may be due to "a change in the muscle itself, probably at the motor end-plate where these drugs act."

***Chloral Hydrate* ←**

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract questionably diminishes resistance to chloral hydrate.

Zárday & Weiner A52,879/34: Anesthesia with morphine in rats, and with chloral hydrate in rabbits was not significantly influenced by pretreatment with thyroxine s.c., one hour before the anesthetics. On the other hand, phenobarbital anesthesia was prolonged by thyroxine pretreatment in rabbits under identical conditions. Similar observations have been made on patients suffering from thyrotoxicosis, in that they are unusually resistant to barbiturates but not to other anesthetics. This selective antagonism is ascribed to interactions between thyroxine and barbiturates at some common receptor site in the midbrain.

Zárday & Weiner: 53,715/35: In rabbits, thyroxine s.c. does not influence the narcotic effect of chloral hydrate given a few hours later. On the other hand, the resistance to phenobarbital rises through the influence of thyroxine under similar conditions.

***Chloralose* ←**

Cheyrol & Quinquaud 3,531/32: In dogs, thyroparathyroidectomy greatly increases sensitivity to chloralose anesthesia.

***Chlordiazepoxide* ← cf. also Table 38**

Winter G71,836/65; F64,465/66; Winter F98,019/68: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazole is increased by T3 or thyroid powder, whereas the narcotic effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects.

Ashford & Ross H2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlor-

promazine, perphenazine, and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Chloroform ←

Hari 40,209/21: Polemic remarks concerning the technique and interpretation of earlier data on the effect of thyroidectomy upon the resistance to cyanides, chloroform, bacterial toxins, and oxygen deficiency.

McIver A 35,431/40: In rats, susceptibility to chloroform poisoning is increased by thyroxine.

Black-Schaffer et al. B 55,142/50: In rabbits, chloroform s.c. produces midzonal necrosis of the liver following pretreatment with thyroid extract. Normal or starved rabbits respond to chloroform with centrilobular necrosis. Presumably, "the hyperthyroid state selectively affects the hepatic midzone qualitatively or quantitatively so as to amplify its sensitivity to chloroform beyond that of the periportal or central zones."

Martin B 88,524/53: In rats, both chloroform and alloxan produce hepatic necrosis and their effect is increased when both agents are given in combination. Thiouracil protects against this form of hepatic necrosis whereas thyroid feeding aggravates it.

Chlorpromazine ←

Ashford & Ross H 2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlorpromazine, perphenazine and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Skobba & Miya G 64,738/69: In rats, the hyperthermia produced by thyroxine or dinitrophenol increases the toxicity of chlorpromazine. Cooling the animals by an air current prevents this increase in toxicity.

Cholesterol ← cf. also *Selye* G 60,083/70, pp. 385, 395.

Suzue et al. 38,509/36: In rabbits, the production of xanthomatous lesions in the liver by a high-fat high-cholesterol diet is increased by thyroidectomy and inhibited by thyroxine.

Steiner et al. B 28,166/48: In dogs, thiouracil greatly enhances the production of atherosclerosis by cholesterol feeding.

Stamler et al. C 81,655/58: In cholesterol-fed chicks, desiccated thyroid, thyroxine, T3 and T2 diminished hypercholesterolemia, but a

definite and consistent suppression of coronary or aortic atherosclerosis was not observed.

Osumi G 34,534/65: In cholesterol-fed rabbits, combined treatment with T3 and 3,5,3'-triiodo-4-acetyl-thyroformic acid (TBF-43) inhibited fatty degeneration of the liver, adrenal and spleen, but did not noticeably influence the atherosomatous changes in the arteries.

Kessler et al. F 89,469/67: In rats fed a high-fat high-cholesterol diet, the resulting increase in hepatic and plasma cholesterol and lipid is not changed by either L- or D-thyroxine but D- or L-T3 diminishes the rise of both values in the serum and increases it further in the liver.

Danielsson & Tchen G 72,327/68 (p. 159): Brief summary of the influence of the thyroid upon cholesterol and bile acid metabolism.

Hamprecht G 69,560/69: Review (7 pp., 153 refs.) on the mechanisms regulating cholesterol synthesis. A special section deals with the effect of thyroid hormones, steroids, epinephrine, norepinephrine and glucagon.

Cholesterol ← *Thyroxine*: *Mitropoulos et al.* G 26,978/65

Cinchophen ← cf. *Table 39*

Clofibrate ←

Azarnoff & Svoboda H 19,856/69: In rats, the proliferation of hepatic microbodies induced by clofibrate is not abolished by thyroidectomy nor does it occur after various other compounds which displace thyroxine from the plasma. "These observations make less tenable the hypothesis that thyroid hormone displacement is the mechanism of action of clofibrate."

Cocaine ← cf. also *Table 40*

Glaubach & Pick 11,431/30: In rabbits, pretreatment with thyroxine increases the fever normally produced by tetrahydro-β-naphthylamine or cocaine to fatal levels.

Glaubach & Pick 6,241/31: Studies in guinea pigs and rabbits on the increase in dibucaine, cocaine and procaine toxicity caused by thyroxine as judged by the resulting temperature variations.

Selye G 70,471/71: In rats, cocaine intoxication is inhibited by PCN, ethylestrenol, CS-1, spironolactone, norbolethone, oxandrolone, prednisolone and estradiol. Triamcinolone and DOC fail to protect and thyroxine actually aggravates cocaine intoxication.

Codeine ←

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract diminishes resistance to codeine.

Anan 24,228/29: In mice, thyroxine increases the toxicity of morphine and heroin but not that of other alkaloids such as ethylmorphine codeine, thebaine, papaverine and narcotine.

Colchicine ← cf. also Table 41

Vollmer & Buchholz A 48,810/30: In mice, thyroxine as well as various other "oxidizing substances" (glucose, lactate, methylene blue etc.) protect against alcohol intoxication. The same substances decrease resistance to colchicine or hydroquinone. Morphine resistance is not influenced.

Selye G60,098/70: In rats, fatal colchicine poisoning can be prevented by spironolactone, CS-1, ethylestrenol and, less constantly, by oxandrolone. Progesterone, norbolethone, prednisolone, triamcinolone, DOC, hydroxydione, estradiol and thyroxine are virtually ineffective in this respect.

Compound MO-911 ←

Carrier & Buday D 11,237/61: In rats, feeding with thyroid extracts greatly augments the lethal effect of a hydrazide (iproniazid) or of a nonhydrazide (N-methyl-N-benzyl-2-propynylamine hydrochloride; 'MO-911') enzyme inhibitor.

MO-911 ← Thyroid extract: Carrier et al. D 11,237/61*

DL-Coniine ← cf. Table 42**Curare ←**

Tabachnick et al. C 50,317/58: In mice, thyroxine increases sensitivity to decamethonium and neostigmine but not to D-tubocurarine or succinylcholine. Rabbits pretreated with thyroxine also become more sensitive to decamethonium. It is tentatively suggested that the motor disturbances associated with hyperthyroidism may be due to "a change in the muscle itself, probably at the motor end-plate where these drugs act."

Croton Oil ← cf. Table 43**Cyanide ←**

Hunt 60,064/05: In mice, thyroid feeding greatly increases resistance to acetonitrile but not to various other cyanides, such as hydrocyanic acid or sodium ferricyanide.

Mansfeld & Müller 35,416/11: In rabbits, thyroidectomy inhibits the protein catabolic effect of exposure to decreased oxygen tension, hydrocyanic acid intoxication or fasting.

Mansfeld 11,881/20: In rabbits and dogs, thyroidectomy diminishes the protein catabolism normally observed after intoxication with hydrocyanic acid, hemorrhage, or hypobaric oxygenation.

Hari 40,209/21: Polemic remarks concerning the technique and interpretation of earlier data on the effect of thyroidectomy upon the resistance to cyanides, chloroform, bacterial toxins and oxygen deficiency.

Gellhorn 16,839/23: In mice, resistance against acetonitrile can be increased not only by thyroid extract but, to a lesser extent, also by extracts of various other tissues. These preparations also augment resistance to potassium cyanide (KCN) and propionitrile, whereas thyroidectomy and orchidectomy have an opposite effect.

Busso 26,684/25: In rats, thyroidectomy decreases sensitivity to KCN, whereas the reverse is true in rabbits.

Tsuru 44,467/33: In rabbits, pretreatment with thyroid extract did not significantly influence resistance to hydrocyanic acid or thiocyanides.

Dietrich & Beutner B 20,412/44: In mice, thiourea and thiouracil interfere with the action of orally administered thyroid powder when the Reid Hunt test is made the basis of observations. In this test, minute amounts of whole thyroid can be detected by their protective effect against otherwise lethal doses of acetonitrile.

Cycloheximide ← cf. also Tables 44, 45

Selye G70,403/70: In rats, cycloheximide intoxication is inhibited by ethylestrenol, CS-1 and spironolactone. Norbolethone, oxandrolone, progesterone, hydroxydione, and prednisolone offer less perfect protection. Triamcinolone, DOC, estradiol and thyroxine have no protective effect.

Cyclophosphamide ← cf. also Table 46

Selye G70,466/70: In rats, cyclophosphamide intoxication can be prevented by PCN, CS-1 and spironolactone. Progesterone, ethylestrenol and norbolethone were slightly active; oxandrolone, DOC, hydroxydione and phenobarbital were inactive, whereas prednisolone, triamcinolone, estradiol and thyroxine actually decreased resistance to this drug, cf. Fig. 22, p. 480.

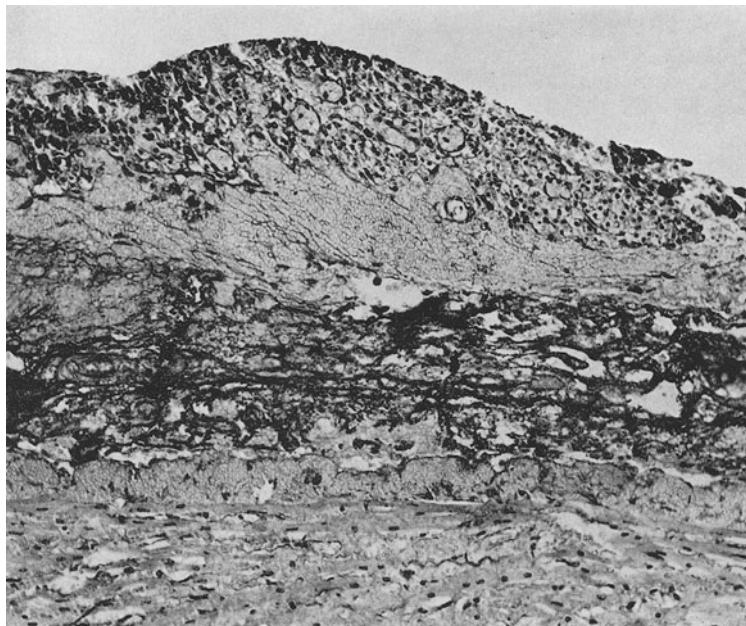


Fig. 22. Effect of thyroxine upon cyclophosphamide intoxication. Hemorrhagic, pericardial exudate in rat given cyclophosphamide after pretreatment with thyroxine. Leucocytes are absent because of the cyclophosphamide-induced atrophy of hemopoietic tissue. PAS X

Cystine ←

György & Goldblatt G71,898/45: In rats kept on a hepatotoxic diet containing large amounts of cystine, the development of liver cirrhosis could be prevented by thiouracil p.o.

Decamethonium ←

Tabachnick et al. C50,317/58: In mice, thyroxine increases sensitivity to decamethonium and neostigmine but not to D-tubocurarine or succinylcholine. Rabbits pretreated with thyroxine also become more sensitive to decamethonium. It is tentatively suggested that the motor disturbances associated with hyperthyroidism may be due to "a change in the muscle itself, probably at the motor end-plate where these drugs act."

Desipramine ← Thyroid extract,
Mouse: Prange et al. F29,162/64*

α,γ -Diaminobutyric Acid ←

Vivanco et al. G43,566/66: In rats α,γ -diaminobutyric acid (DBA) produced a neurologic syndrome in the rat. "The animals became

irritable and screamed when touched. They moved the head from side to side in the manner of a bear and leaped like kangaroos or frogs. Sometimes they got up on the rear legs with simultaneous quivering of the forearms. They showed excessive salivation. In the preagonal state they presented paresis or paralysis of the hind limbs and motor incoordination. The 'swimming test' was always negative and they did not show circling movements or backward gait as in the IDPN intoxication." Pretreatment with thyroxine prevents these changes as it does the clinically different ECC syndrome (excitation, choreiform and circling movements) elicited by β,β' -iminodipropionitrile (IDPN). DBA enters the brain substance in unpretreated but not in thyroxine-treated rats. Possibly the toxic compound is destroyed before it can enter the brain.

Dibucaine ←

Glaubach & Pick 6,241/31: Studies in guinea pigs and rabbits on the increase in dibucaine, cocaine and novocaine toxicity caused by thyroxine as judged by the resulting temperature variations.

Digitalis ← cf. also Selye G60,083/70, p. 408.

Ghedini & Ollino A 21,128/14: Brief mention of observations on rabbits showing that pretreatment with thyroid extract augments the hemodynamic actions of digitalin in the rabbit.

Freund A 26,153/32: Studies on the effect of thyroidectomy or pretreatment with thyroxine or insulin upon the in vitro metabolic changes induced by digitalis compounds in the cat's heart.

Kinsell et al. A 37,369/42: Experiments on guinea pigs and mice suggested that "therapeutic dosage of cardiac steroid-glycosides prevents a weight loss in thyroxin-treated animals similar to that obtained with adrenal cortical hormone and desoxycorticosterone acetate. Larger dosage of these cardiac glycosides either fails to modify such weight loss or actually increased it."

Dearing et al. C 41,482/43: In cats, thyroxine aggravates the myocardial lesions produced by various digitalis alkaloids.

Dearing et al. B 53,571/50: In cats, various digitalis preparations produce myocardial fiber necrosis and inflammation. Pretreatment with thyroxine sensitizes the animals to these lesions.

Rosen & Moran D 65,414/63: In dogs, the positive inotropic response to ouabain was decreased by thyroxine. The arrhythmia-producing and lethal effect of large doses of this glycoside were delayed by thyroidectomy but not remarkably influenced by thyroxine. The literature on the influence of clinical hyper- and hypothyroidism upon digitalis intoxication is reviewed.

Phansalkar et al. H 20,555/69: In mice, pretreatment with thyroxine greatly increases mortality from subsequent digoxin administration. Reserpine protects against this intoxication. It is suggested that digoxin toxicity is mediated through a catecholamine mechanism.

Selye G 70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Selye PROT. 33541,34074: In rats, PCN is highly efficacious in preventing digitoxin poisoning, even after parathyroidectomy, thyroparathyroidectomy or concurrent treatment with propylthiouracil (PTU). No pro-

tection was obtained by thyroidectomy, parathyroidectomy or treatment with PTU, thyroxine, parathyroid extract or calcitonin. Apparently, the goitrogenic effect of PCN plays no indispensable role in its cataleptic action, cf. Table 124, p. 482.

Digitoxin ← cf. also Tables 47—50

Diisopropylfluorophosphate (DFP) ←

Schreiber C 3,482/54: In mice, pretreatment with methylthiouracil increases resistance against diisopropylfluorophosphate (DFP).

"DFP" ← cf. also Table 52

Dinitrophenol ←

Glaubach & Pick 30,481/34: In rabbits, the lethal effect of dinitrophenol, and of several of its pyrogenic derivatives, is greatly aggravated by pretreatment with thyroxine.

Dihydroxyphenylalanine ←

Samiy B 68,269/52: Both in rats and in rabbits, DOPA produced sustained hypertension following pretreatment with thyroxine. Presumably, thyroid hormone enhances the decarboxylation of DOPA to the pressor agent hydroxytyramine.

Halpern et al. G 63,588/63: In mice, thyroxine pretreatment diminishes resistance to amphetamine and DL-dopa, especially under conditions of crowding.

Diphenylhydantoin ← cf. Table 53

Dipicrylamine ← cf. Table 54

Disulfiram ←

Lecoq et al. B 66,406/51: In rats, the toxic effects of ethanol and its metabolites, pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Dye ←

Aterman & Howell C 63,343/59: In rats, the biliary excretion of bromsulphthalein is delayed after destruction of the thyroid by ¹³¹I. This defect is corrected by treatment with thyroid extract.

Table 124. Role of the thyroparathyroid apparatus in the antidigitoxin effect of PCN

Treatment ^a	Convulsions ^b (Positive/Total)	Mortality ^b (Dead/Total)	Mean Survival (Days)
None	14/15	15/15	4
PCN	1/10 ***	0/10 ***	∞
Thyroidectomy	12/12 NS	12/12 NS	3
Thyroidectomy + PCN	1/12 ***	0/12 ***	∞
Parathyroidectomy	9/9 NS	8/9 NS	3½
Parathyroidectomy + PCN	0/10 ***	2/10 ***	4
PTU	10/10 NS	7/10 NS	3½
PTU + PCN	0/10 ***	0/10 ***	∞
Thyroxine	10/10 NS	10/10 NS	2½
Parathyroid extract	10/10 NS	9/10 NS	3½
Calcitonin	10/10 NS	10/10 NS	3

^a The rats of all groups were given digitoxin 2 mg in 1 ml water, p.o./day on 10th day ff. PTU 3 mg in 0.1 ml DMSO, i.p. x2/day; PCN 0.1 mg in 1 ml water, p.o. x2/day; thyroxine 100 µg in 0.2 ml water NaOH, s.c./day and surgery on the 1st day. Parathormone 20 I.U. in 0.2 ml s.c. x2/day and calcitonin 10 µg in 0.5 ml water, i.p. x3/day on the 9th day.

^b The severity of the convulsions was estimated on the 13th day and mortality was listed on the 15th (Statistics Fisher & Yates).

For further details on technique of tabulation cf. p. VIII.

Dolgova & Dolgov G33,058/64: In rats, the organ distribution of parenterally administered neutral red is considerably modified by pretreatment with thyroid extract. Increased dye deposition was noted in the liver, spleen, and skeletal muscle, whereas in the brain and testes dye-uptake was reduced.

Kulcsár et al. H24,478/70: In rats, thyroxine increases, whereas thyroidectomy decreases, the hepatotoxicity of CCl₄ as judged by BSP elimination.

Emetine ← cf. Table 55

Ephedrine ←

Halpern et al. F24,137/64; F27,643/64: In mice, the toxicity of amphetamine and ephedrine is increased by pretreatment with thyroxine not only—as had been previously shown—when several animals are kept together in a jar, but also when they are kept in solitary cages.

EPN ← cf. Pesticides

Ergot ←

Griffith Jr. & Comroe A33,738/40: In rats, pretreatment with thyroxine s.c. increases mortality and the incidence of tail necrosis following s.c. injections of ergotamine tartrate.

Wells & Anderson G74,995/50: In rats, the production of tail gangrene by ergotamine is not influenced by propylthiouracil but facilitated by thyroxine. “It is assumed that thyroxin acts, not by altering the resistance of the tissues to vascular occlusion, nor by sensitizing the vascular musculature to ergotamine, but by prolonging the action of the alkaloids, possibly by interfering with their elimination or destruction.”

Ethanol ←

Preusse 26,352/33: In mice, thyroxine or thyroid powder causes only a moderate increase in resistance to ethanol.

Vollmer & Buchholz A48,810/30: In mice, thyroxine as well as various other “oxidizing substances” (glucose, lactate, methylene blue etc.) protect against alcohol intoxication. The same substances decrease resistance to colchicine or hydroquinone. Morphine resistance is not influenced.

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites, pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol

intoxication. [Statistically evaluated data are not presented (H.S.).]

Aragona & Barone B92,455/53: In rats, methylthiouracil aggravates the hepatic lesions produced by ethanol intoxication.

Choisy & Potron H28,010/68: In rabbits, pretreatment with thyroxine accelerates the oxidation of ethanol and its clearance from the blood.

Ether ←

Rutsch 7,744/33: In guinea pigs, thyroidectomy decreases, whereas thyroxine pretreatment increases, resistance to ether, paraldehyde or tribromoethanol anesthesia. These findings are ascribed to changes in the responsiveness of the brain.

Ethylene Glycol ← cf. Table 56

Ethylmorphine ← cf. Table 57

Flufenamic Acid ← cf. Table 58

Fluoride ←

Phillips et al. 34,798/35: In chicks, combined treatment with thyroid extract and NaF is particularly toxic.

Bixler et al. E99,118/56: In rats with hypothyroidism induced by ^{131}I , the protective effect of fluorine against dental caries is diminished.

Fluphenazine ← cf. Table 59

Ganglioplegics ← cf. Tables 61, 62

Glutethimide ← cf. Table 63

Glycerol ← cf. Table 64

Guanidine ←

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract does not influence resistance to guanidine.

Spinelli 10,086/31; 7,409/32: In guinea pigs, thyroidectomy decreases resistance to the lethal effects of guanidine intoxication. Subsequent administration of thyroid extract restores the resistance to normal.

Parhon & Werner 34,844/35: In dogs, guinea pigs and rabbits, thyroparathyroidectomy causes only a moderate increase in sensitivity to methylguanidine.

Halothane ←

Nikki G71,573/69: In mice, shivering and hypothermia during halothane anesthesia is diminished following pretreatment with thyroxine.

Heroin ←

Anan 24,228/29: In mice, thyroxine increases the toxicity of morphine and heroin but not that of other alkaloids such as ethylmorphine, codeine, thebaine, papaverine and narcotine.

Hydroquinone ← cf. also Table 65

Vollmer & Buchholz A48,810/30: In mice, thyroxine as well as various other "oxidizing substances" (glucose, lactate, methylene blue etc.) protect against alcohol intoxication. The same substances decrease resistance to colchicine or hydroquinone. Morphine resistance is not influenced.

N-(p-Hydroxyphenyl) glycine ←

Li & Sos H30,786/68: In rats, N-(p-hydroxyphenyl)glycine fails to exert its usual pressor effect after thyroidectomy.

Imipramine ← cf. also Table 66

Prange & Lipton D42,869/62: In mice, pretreatment with thyroxine greatly increases the initial convulsive actions and the terminal mortality of imipramine intoxication.

Prange et al. D62,707/63: In mice pretreatment with propylthiouracil increases resistance to imipramine, whereas hyperthyroidism has an opposite effect.

Winter G71,836/65: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazole is increased by T3 or thyroid powder, whereas the narcotic effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects. [The experimental conditions are not described in sufficient detail to evaluate these findings (H.S.).]

Winter F64,465/66; F98,019/68: In mice, pretreatment with thyroid extract p.o. increases the toxicity of reserpine, chlordiazepoxide, imipramine and amphetamine.

Ashford & Ross H2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlorpromazine, perphenazine and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Prange Jr. et al. G76,612/70: In man, the antidepressive effect of imipramine is enhanced by TTH as well as by T3. Earlier literature is cited.

Prange et al. G69,595/69: In retarded, depressed patients, small doses of T3 enhanced the therapeutic effect of imipramine.

Prange et al. H31,796/70: In depressed patients, T3 increases the therapeutic effect of imipramine.

Imipramine ← Thyroid extract,
Mouse: Prange et al. D42,869/62*

Indomethacin ← cf. also Table 67

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Iodides ← cf. Selye G60,083/70, p. 407

Iproniazid ←

Carrier & Buday D11,237/61: In rats, feeding with thyroid extracts greatly augments the lethal effect of a hydrazide (iproniazid) or of a nonhydrazide (N-methyl-N-benzyl-2-propynylamine hydrochloride; 'MO-911') enzyme inhibitor.

Carrier & Buday E28,887/63: In rats, the toxic effects of the MAO inhibitors, pargyline and iproniazid are increased by pretreatment with desiccated thyroid.

Isoniazid ←

Hunt & Carlton F3,186/64: In Pekin ducks, combined administration of semicarbazide and isoniazid p.o. produces a neurolathyrysm-like syndrome which is not significantly influenced either by thiouracil or by DL-thyroxine.

Isoproterenol ← cf. also Selye C92,918/61, pp. 117, 123; G60,083/70, pp. 405, 406.

Chappel et al. C71,409/59: In rats, thyroxine aggravates, whereas thyroidectomy or propylthiouracil treatment inhibits the development of myocardial lesions following injection of isoproterenol.

Lathyrogens ← cf. also Selye C92,918/61, p. 137; G60,083/70, p. 357.

DUCK

Hunt & Carlton F3,186/64: In Pekin ducks, combined administration of semicarbazide and isoniazid p.o. produces a neurolathyrysm-like syndrome which is not significantly influenced either by thiouracil or by DL-thyroxine.

RAT

Selye & Bois C18,280/56: In rats, the osteolathyrysm produced by *Lathyrus odoratus* seeds is aggravated by STH and inhibited by cortisol. Combined treatment with DOC + uninephrectomy + NaCl resulted in dissecting aneurysms of the aorta. Very small doses of thyroxine or estradiol were without effect upon this form of lathyrysm.

Daster C36,068/57: Brief mention of unpublished observations indicating that in rats, osteolathyrysm produced by APN is not inhibited by cortisone or thyroxine, but aggravated by STH.

Diaz et al. O50,497/57: Thyroxine inhibits the osteolathyrysm produced in rats by methyleneaminoacetonitrile (MAAN). Estrogens allegedly have a similar, though somewhat less pronounced, effect. [The authors actually tested only estrone in combination with progesterone (H.S.).]

Ponseti E54,643/57: In rats, the osteolathyrism changes produced by AAN are more readily inhibited by T3 than by thyroxine.

Selye C25,013/57: The osteolathyrysm produced in rats by AAN is slightly aggravated by thyroparathyroidectomy, and suppressed by large doses of thyroxine. "An amount of ACTH that more than doubles the weight of the adrenals and causes pronounced thymus atrophy also inhibits the effect of AAN, but fails to prevent it completely. This is all the more noteworthy because comparatively small doses of cortisol can totally prevent such bone lesions. Extensive partial hepatectomy greatly increases the effect of AAN upon the bones."

Selye C31,790/57: In rats, osteolathyrysm produced by AAN is inhibited by thyroxine, cortisol and estradiol but aggravated by STH even after adrenalectomy.

Selye C36,049/57: In rats, the ocular changes produced by IDPN are even more readily prevented by thyroxine than other manifestations of neurolathyrysm.

Strong et al. G61,885/58: In rats, T3 or iodinated casein offered only slight protection against APN poisoning, "although skeletal changes were somewhat delayed and reduced in severity, possibly because of slower growth."

Diaz et al. D99,329/58: In rats, the osteolathyrysm produced by MAAN is mildly inhibited by progesterone and estrone, completely prevented by thyroxine and aggravated by thyroidectomy.

Ponseti & Aleu C61,715/58: In rats with lathyrysm produced by AAN, bone fractures

produce unusually large calluses which do not ossify well. T₃ diminishes the size of the callus and improves its ossification.

Selye C 36,069/58: In rats, the ECC syndrome (excitement, choreiform movements, and circling) normally produced by IDPN is inhibited by thyroxine. Thyroidectomy had no effect, but since the controls were 100% positive, an aggravation could not have been noted.

Ponseti C 68,050/59: In rats, the lathyrine bone lesions produced by AAN were strongly suppressed by triiodothyronine and thyroxine, whereas those elicited by APN were much less evidently inhibited by these hormones. "Corticosterone and cortisone suppressed only slightly the lesions produced by aminoacetonitrile in rats."

Ponseti C 78,321/59: In rats, T₃ is about 50 times as potent as thyroxine in suppressing osteolathyrism after treatment with AAN.

Pyörälä et al. G 67,833/59: Dissecting aneurysms of the aorta developed in 40% of immature rats fed *Lathyrus odoratus*. The media was remarkably thickened and the ground substance showed increased metachromasia and PAS reaction. This response was suppressed by cortisone and thyroxine but not by ACTH, TTH or DOC at the doses employed.

Gabay et al. D 98,867/61: In rats, the osteolathyrism produced by MAAN is associated with a considerable increase in bone hexosamine. This change is more effectively inhibited by thyroxine than by cortisone. Both hormones are virtually ineffective in protecting against osteolathyrism produced by the feeding of *Lathyrus odoratus* seeds.

Khogali D 10,840/61: In rats, the diminished breaking stress and stiffness of the bones, characteristic of lathyrism induced by APN, can be counteracted both by L- and by D-T₃. Since both isomers are equally effective in this respect, it is considered unlikely that their antilathyrine property depends upon classic thyroid hormone properties.

Selye & Cantin C 88,878/61: In rats, the osteolathyrism produced by AAN is inhibited by thyroxine and cortisol but aggravated by STH. The cardiac infarcts elicited in rats by ligature of the descending branch of the left coronary artery are often transformed into rupturing cardiac aneurysms under the influence of AAN. The incidence of these cardiac ruptures is augmented by cortisol and DOC, but not significantly influenced by thyroxine and STH. Evidently there is no direct rela-

tionship between the skeletal and the cardiac lesions under these circumstances.

Vivanco et al. D 10,627/61: Thyroxine prevents the osteolathyrism produced by MAAN but not that elicited by a *Lathyrus odoratus* diet.

Vivanco et al. D 15,606/61: In rats, the neurolathyrism produced by IDPN as well as the associated histologic changes in the central nervous system are prevented by thyroxine.

Aschkenasy D 30,881/62: In rats, lathyrism produced by AAN is inhibited by thyroxine and aggravated by propylthiouracil.

Glickman et al. E 24,104/63: In rats, the dental changes produced by AAN are aggravated following partial hepatectomy and thyroidectomy, reduced by ACTH and almost completely abolished by thyroxine.

Lalich & Turner G 44,676/67: In rats fed APN in combination with cottonseed meal, there occurred severe diarrhea, colonic dilatation and herniation in the costo-vertebral angle. These changes were uninfluenced by T₃.

Morcos F 80,855/67: In rats, thyroxine did not prevent the development of the ECC syndrome following injection of IDPN but only delayed its onset.

Alper & Ruegamer H 17,023/69: In rats which developed lathyrism under the influence of semicarbazide, the antithyroid agent methimazole prevented the accumulation of chondroitin sulfate in the aorta.

AAN ← cf. also Table 73

Lead ←

Gabbiani et al. G 46,731/68: In rats, pretreatment with thyroxine or calcitonin inhibits the soft-tissue calcification and osteitis fibrosa induced by parathyroid extract overdosage. When both hormones are given simultaneously their effects are summated. Calcitonin, but not thyroxine, inhibits the local calcergy (induced by intravenous injection of lead acetate followed by topical administration of polymyxin) and the hypercalcemia produced by a single injection of lead acetate.

LSD ← cf. Table 74

Magnesium ←

Forbes G 30,402/65: In rats, thyroxine prevents the nephrocalcinosis of magnesium deficiency.

Jasmin E 7,631/68: In rats, certain manifestations of the magnesium-deficiency syn-

drome are inhibited by cortisol, hypophysectomy or thyroparathyroidectomy.

Jacob & Forbes G69,934/69: In rats, nephrocalcinosis produced by magnesium deficiency is inhibited by approximately equal amounts of D- or L-thyroxine, but only if D-thyroxine is administered frequently enough to offset its more rapid metabolism in the tissue.

Forbes G81,277/71: In rats, the renal calcification produced by magnesium deficiency is prevented by thyroxine and aggravated by thyroid deficiency or injection of adenine. Such metabolic stimulators as Na-salicylate or 2,4-dinitrophenol are without effect.

Mechlorethamine ← cf. Table 75

Meperidine ←

Schrogie & Solomon C43,019/66: In mice, the metabolism of bishydroxycoumarin was markedly inhibited by both L- and D-thyroxine. The demethylation of meperidine was likewise inhibited by both isomers but particularly by D-thyroxine. L-thyroxine also increased the lethal effect of meperidine over dosage. Pentobarbital sleeping time was prolonged in mice treated with either L- or D-thyroxine but the latter was more active in this respect.

Mephenesin ← cf. Table 76

Meprobamate ← cf. also Table 77

Selye & Solymoss G70,402/70: Although in rats meprobamate intoxication is counteracted by catatonic steroids, thyroxine actually aggravates it.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Mercury ← cf. Tables 78—80

Methadone ← cf. also Table 82

Sung & Way B91,323/53: Rats treated with thiouracil or methimazole showed tolerance to toxic actions of methadone (absence of general depression and body rigidity). In thyroidectomized animals, the increase in pain-threshold was also diminished. Feeding of thyroid powder exerted opposite effects. Liver slices from thiouracil and thyroid-fed rats metabolized methadone more slowly than those from controls. Tissue levels of methadone were also increased by both these agents. However, total

urinary and fecal excretion of methadone was essentially the same in all groups.

n-Methylaniline ← cf. Table 83

Methylphenidate ←

Fregly & Black F15,674/64: In rats, pretreatment with propylthiouracil appeared to decrease the responsiveness to methylphenidate (given in the diet) as judged by the increased activity level induced by exposure to cold. However, "this difference in activity level is probably associated with differences in the food (and drug) intakes of the two groups."

Selye PROT. 27955: In rats, pretreated with thyroxine, methylphenidate produced temporary but very severe paralysis of the hind legs when given at dose levels which in nonpretreated controls caused only excitation.

α-Methyl-p-tyrosine ←

Moore G36,616/65: In mice, pretreatment with T3 greatly increases sensitivity to the lethal effect of amphetamine. "Chlorpromazine, phenoxybenzamine, and propranolol pretreatment reduced the lethality of d-amphetamine in hyperthyroid mice while α-methyl-m-tyrosine, α-methyl-p-tyrosine, and reserpine pretreatment did not. The toxicity of α-methyl-m-tyrosine was enhanced in hyperthyroid mice."

Methyprylon ← cf. Table 84

Morphine ←

Hunt 49,716/07: Comparative studies on the effect of thyroid extract upon the acetonitrile and morphine resistance of mice, rats and guinea pigs.

Hunt & Seidell 50,346/09: In mice, rats and guinea pigs, pretreatment with thyroid extract diminishes resistance to morphine.

Olds Jr. 34,544/10: In rats, thyroidectomy does not alter resistance to morphine.

Busso 26,684/25: In rats, thyroidectomy does not change the resistance to epinephrine or phenol. Morphine appears to be slightly more toxic to thyroidectomized than to intact rats but the results were irregular.

Anan 24,228/29: In mice, thyroxine increases the toxicity of morphine and heroin but not that of other alkaloids such as ethylmorphine, codeine, thebaine, papaverine and narcotine.

Lund & Benedict A14,206/29: In rabbits, morphine causes a more pronounced drop in

the BMR in the absence than in the presence of the thyroid. Morphine does not influence the rise in BMR induced by a thyroid extract.

Glaubach & Pick 11,431/30: In guinea pigs, pretreatment with thyroxine diminishes resistance against morphine.

Vollmer & Buchholz A 48,810/30: In mice, thyroxine as well as various other "oxidizing substances" (glucose, lactate, methylene blue etc.) protect against alcohol intoxication. The same substances decrease resistance to colchicine or hydroquinone. Morphine resistance is not influenced.

Zárday & Weiner A 52,879/34: In rats, morphine, and in rabbits chloral hydrate anesthesia were not significantly influenced by pretreatment with thyroxine s.c., one hour before the anesthetics. On the other hand, phenobarbital anesthesia was prolonged by thyroxine pretreatment in rabbits under identical conditions. Similar observations have been made on patients suffering from thyrotoxicosis in that they are unusually resistant to barbiturates but not to other anesthetics. This selective antagonism is ascribed to interactions between thyroxine and barbiturates at some common receptor site in the midbrain.

Zárday & Weiner 53,715/35: In rats, pretreatment with thyroxine s.c. does not influence the narcotic action of morphine given s.c. a few hours later.

Swann 80,669/41: In rats, thyroideectomy does not alter the morphine withdrawal symptoms.

Bhagat F 9,444/64: In mice, pretreatment with thyroxine increased the analgesic action of morphine.

Cochin & Sokoloff D 29,487/60: "The effect of in vivo administration of L-thyroxin on in vitro N-demethylation of morphine by rat-liver enzyme preparations from normal and morphine-treated rats has been investigated. Thyroxin given 7 days to otherwise untreated control animals has no effect on N-demethylating activity, but after 10—14 days it significantly depresses this activity. Administration of thyroxin for 7 days prior to and during morphine withdrawal reduces further the enzyme activity already markedly depressed after chronic administration of morphine, and prevents almost completely recovery of activity which occurs some 8—10 days after morphine withdrawal."

Winter G 71,836/65: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazol is increased by T₃ or thyroid powder, whereas the narcotic

effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects. [The experimental conditions are not described in sufficient detail to evaluate these findings (H.S.).]

Morphine ← Thyroxine + Morphine: *Cochin et al. D 29,487/60*

a-Naphthylisothiocyanate ← cf. Table 85

Navadel ← cf. *Dioxathion under Pesticides*

Neostigmine ←

Tabachnick et al. C 50,317/58: In mice, thyroxine increases sensitivity to decamethonium and neostigmine but not to D-tubocurarine or succinyl choline. Rabbits pretreated with thyroxine also become more sensitive to decamethonium. It is tentatively suggested that the motor disturbances associated with hyperthyroidism may be due to "a change in the muscle itself, probably at the motor end-plate where these drugs act."

Nicotine ← cf. also Table 86

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract does not influence resistance to nicotine.

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine and atropine but augments sensibility to pilocarpine and guanidine.

Gogolák et al. G 51,384/67: In hypothyroid (¹³¹I, methylthiouracil, NaClO₄) rats, higher doses of nicotine are required to produce hippocampal-seizure discharges with the typical modifications in EEG than in intact animals. The comparable effect of pentylenetetrazol is not modified by hypothyroidism.

Selye G 70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Nikethamide ← cf. Table 87

p-Nitroanisole ← cf. Table 88

Nitrogen Dioxide ←

Fairchild & Graham D 50,574/63: In mice and rats, mortality induced by exposure to respiratory irritants such as ozone or nitrogen dioxide is inhibited by thioureas or thyroidectomy but enhanced by thyroxine or T₃.

Dinitrophenol, in doses known to elevate the BMR, did not significantly affect mortality under these conditions.

Nitrogen Mustard ←

Connors & Elson G2,440/62: In rats, thioureas reduce the toxicity of certain radiomimetic alkylating agents. The same is true of other compounds containing thiol groups.

Nitrous Oxide ←

Rummel et al. D89,013/57: In guinea pigs and rabbits, thyroxine increases the threshold for N₂O anesthesia, whereas dinitrophenol has no such effect. Contrary to expectations, methylthiouracil also failed to affect the N₂O anesthesia threshold.

Rummel C79,429/59: In guinea pigs and rats, thyroxine increases, whereas thyroidectomy decreases, the threshold for N₂O anesthesia. Dinitrophenol is ineffective. DOC lowers, whereas cortisone raises, this anesthesia threshold.

Rummel & Wellensiek D96,909/68: In rats, the N₂O anesthesia threshold is diminished by thyroidectomy and restored to normal by thyroxine but not by dinitrophenol.

Nortriptyline ←

Ashford & Ross H2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlorpromazine, perphenazine and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Novocaine ←

Glaubach & Pick 6,241/31: Studies in guinea pigs and rabbits on the increase in dibucaine, cocaine and novocaine toxicity caused by thyroxine as judged by the resulting temperature variations.

Octamethyl Pyrophosphoramide ← cf. Pesticides

Oxalate ←

Kochmann 55,946/34: In mice, fatal intoxication with Na-oxalate can be prevented by parathyroid extract in a dose-dependent manner suitable for bioassays.

Ozone ←

Fairchild & Stokinger D4,088/61; Fairchild & Graham D56,574/63: In mice and rats, mortality induced by exposure to respiratory irritants such as ozone or nitrogen dioxide is inhibited by thioureas or thyroidectomy but enhanced by thyroxine or T3. Dinitrophenol, in doses known to elevate the BMR, did not significantly affect mortality under these conditions.

Fairchild G71,531/63: Review (6 pp., 26 refs.) on the effect of thyroidectomy, thioureas, thyroid hormones, glucocorticoids and hypophysectomy upon the resistance of various species to inhaled irritants especially ozone.

Paraldehyde ←

Rutsch 7,744/33: In guinea pigs, thyroidectomy decreases, whereas thyroxine pretreatment increases, resistance to ether, paraldehyde or tribromoethanol anesthesia. These findings are ascribed to changes in the responsiveness of the brain.

Paraphenylenediamine ←

Meissner E52,567/19: The head and neck edema produced by paraphenylenediamine in the rabbit is not prevented by epinephrine, posterior pituitary extract or thyroid extract.

Pargyline ←

Carrier & Buday E28,887/63: In rats, the toxic effects of the MAO inhibitors, pargyline and iproniazid are increased by pretreatment with desiccated thyroid.

Paroxypropionine ←

Scharf et al. C91,620/60: In rats, the degenerative changes produced in the pituitary by p-hydroxypropiophenone (paroxypropionine or POP) are aggravated by methylthiouracil.

Pentachlorophenol ←

Pasley et al. G67,522/68: In cichlid fish, the toxic effect of pentachlorophenol (a herbicide, molluscicide and lumber preservative) is counteracted by thyroxine.

Pentylenetetrazol ← cf. also Table 89

Woodbury et al. B68,423/52: In rats, brain excitability (pentylenetetrazol, EST) decreases following thyroidectomy or treatment with

propylthiouracil and increases after thyroxine pretreatment. There are however certain differences between thyroidectomy and propylthiouracil as regards the recovery time from electroshock seizures and their relative effect upon extensor and flexor components.

Pfeifer et al. D12,952/60: In rats, the convulsive effect of "Pentametazol" [presumably pentylenetetrazol (H.S.)] is diminished one hour after administration of thyroxine, but increased 18 hrs later. A corresponding biphasic response is also noted with regard to the EST. In mice, the increased motility induced by amphetamine is also inhibited during the first hour after thyroxine treatment. The possible biochemical reasons for this "negative tendency" during the early phase of thyroxine action are described.

Winter G71,836/65: In mice, the toxicity of amphetamine, imipramine, chlordiazepoxide and pentylenetetrazol is increased by T₃ or thyroid powder, whereas the narcotic effect of amobarbital and morphine is decreased. Methylthiouracil has, in general, opposing effects. [The experimental conditions are not described in sufficient detail to evaluate these findings (H.S.).]

Gogolák et al. G51,384/67: In hypothyroid (¹³¹I, methylthiouracil, NaClO₄) rats higher doses of nicotine are required to produce hippocampal-seizure discharges with the typical modifications in EEG than in intact animals. The comparable effect of pentylenetetrazol is not modified by hypothyroidism.

Pfeifer et al. G65,057/68: In mice, thyroxine facilitates the production of convulsions by pentylenetetrazol and electroshock. These effects are inhibited by various amphetamine derivatives.

Pentylenetetrazol ← Thiouracil,
Mouse: Wenzel et al. G76,357/55*

Peptone ←

Houssay & Cisneros 26,936/25: In dogs sensitized after thyroidectomy, subsequent anaphylactic shock is diminished. Thyroidectomized dogs are also comparatively insensitive to peptone shock.

Czarnecki & Kiersz D15,579/61: In dogs, shock produced by trypan blue or peptone injection is more powerfully inhibited by thyroparathyroidectomy than by thyroidectomy.

Perchlorates ← cf. also Table 90

Bajusz & Selye C64,511/59: C57,180/59;
Selye C61,814/59: The spastic muscular con-

tractions (with positive "flick-test") produced by NaClO₄ in the rat can be inhibited by cortisol or triamcinolone, and aggravated by DOC or Me-Cl-COL. Thyroparathyroidectomy or parathyroidectomy exerts a sensitizing effect. Triamcinolone also protects the dog against the syndrome produced by heavy overdosage with NaClO₄. Methyltestosterone, estradiol and progesterone did not significantly affect the response of the rat to NaClO₄.

Perphenazine ←

Ashford & Ross H2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlorpromazine, perphenazine and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Pesticides ← cf. also Tables 91—99

Byerrum B1,322/46: In rats, iodine given either as Lugol's solution or as KI protects against ANTU poisoning.

Byerrum & DuBois B3,076/47: In rats, ANTU poisoning can be prevented by KI p.o. but very little protection is offered to thyroidectomized rats by the administration of iodine. Desiccated thyroid fed for 2 days offered no protection against ANTU.

Meyer & Karel B18,102/48: Of 25 compounds tested only KI and 1-thiosorbitol were unequivocally successful in preventing lethal pulmonary edema and pleural effusion in ANTU-treated rats. Organic iodides (diiodotyrosine, cetyl iodide, n-decyl iodide, amyliodide, and iodoacetic acid) as well as iodine were ineffective.

Carroll & Noble B32,718/49: In rats, resistance to ANTU can be produced not only by pretreatment with ANTU itself but also by previous administration of other thioureas. "Neither the anti-thyroid potency nor the acute toxicity of these substances is directly related to their ability to impart resistance." However, resistance to ANTU is also found in rats fed on certain goitrogenic diets, especially those containing seeds of the brassica species.

Wassermann et al. G74,485/69: In rats, hepatic changes induced by p,p'-DDT are aggravated following thyroidectomy and the storage of p,p'-DDT, o,p'-DDT and dieldrin is increased.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxa-thion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia),

meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Selye G70,435/70: In rats, ethylestrenol, CS-1, spironolactone, and norbolethone counteract the lethal effects of ethion, dioxathion, EPN, Guthion and parathion. To a lesser extent, this is also true of oxandrolone, prednisolone and progesterone. Triamcinolone, desoxycorticosterone, hydroxydione, estradiol, and thyroxine offer no consistent protection against these pesticides. DDT is much more resistant against detoxication by even the most powerful catatotoxic steroids.

Selye et al. G70,457/70: In rats, ethylestrenol, CS-1, spironolactone and norbolethone fail to alter sensitivity to OMPA, although these typical catatotoxic steroids have previously been shown to induce hepatic microsomal enzymes and to detoxify numerous other pesticides. This is of interest because catatoxic barbiturates greatly increase the toxicity of OMPA, presumably by transforming it into a more toxic metabolite. On the other hand, estradiol, estrone and stilbestrol, which have no typical catatotoxic actions, considerably increase OMPA toxicity in ovariectomized rats. "The protective effect of catatoxic steroids is presumably due to their structural characteristics and is independent of other pharmacologic actions. Conversely, sensitization to OMPA depends more upon the estrogenic action of compounds than upon their chemical structure, since stilbestrol, a non-steroidal estrogen, is also highly effective in this respect." Prednisolone, triamcinolone, progesterone, DOC, hydroxydione and thyroxine fail to influence OMPA toxicity.

Selye PROT. 31612: In mice, the lethal effect of dioxathion is powerfully inhibited by ethylestrenol, norbolethone, prednisolone and estradiol, moderately by CS-1 and oxandrolone, but not influenced by spironolactone, progesterone, triamcinolone, DOC, hydroxydione and thyroxine.

DDT ← Thyroidectomy: Wassermann et al. G74,485/69*

Phenol ←

Hunt & Seidell 50,346/09: In mice, pre-treatment with thyroid extract does not influence resistance to phenol.

Busso 26,684/25: In rats, thyroidectomy does not change the resistance to epinephrine or phenol. Morphine appears to be slightly more

toxic to thyroidectomized than to intact rats but the results were irregular.

***Phenylramidol* ← cf. Table 100**

***Phosphates* ←**

Selye C38,627/58: In rats the nephrocalcinosis produced by a dietary excess of NaH_2PO_4 is inhibited both by thyroparathyroidectomy and by excess thyroxine administration.

Cantin F5,681/64: The nephrocalcinosis produced in rats by combined treatment with NaH_2PO_4 + either estradiol or DOC is prevented by parathyroidectomy or thyroparathyroidectomy, and in either case additional treatment with thyroxine prevents nephrocalcinosis.

Meyer & Forbes G53,688/67: In rats kept on a high-phosphate diet, nephrocalcinosis is decreased by thyroxine and increased by prophythiouracil.

***Phosphorus* ←**

Selye & Mishra C40,183/58: In the rat, mortality and hepatic degeneration produced by elementary yellow phosphorus is inhibited by thyroxine and aggravated by thyroidectomy. The associated osteosclerosis was not affected under the conditions of this experiment.

***Physostigmine* ← cf. also Table 110**

Selye G70,435/70: In rats, intoxication with physostigmine was diminished by ethylestrenol, CS-1, spironolactone, and prednisolone, but aggravated by estradiol and thyroxine. Norbolethone, oxandrolone, progesterone, triamcinolone, DOC, and hydroxydione had no significant effect.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxathion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

***Picrotoxin* ← cf. also Table 102**

Hunt & Seidell 50,346/09: In mice, pre-treatment with thyroid extract does not influence resistance to picrotoxin.

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine and atropine but augments sensibility to pilocarpine and guanidine.

Selye G70,428/70: In rats, ethylestrenol powerfully inhibits the toxicity of digitoxin, nicotine, indomethacin, phenindione, dioxa-thion, EPN, physostigmine, hexobarbital, cyclopental, thiopental, DOC (anesthesia), meprobamate and picrotoxin. Thyroxine increases the toxicity of many of these drugs and inhibits the protective effect of ethylestrenol.

Pilocarpine ←

Spinelli 10,086/31: In guinea pigs, thyroidectomy increases the resistance to histamine, acetonitrile, picrotoxin, aconitine, epinephrine, nicotine and atropine but augments sensibility to pilocarpine and guanidine.

Piperidine ← cf. Table 103

Potassium ← cf. also *Selye C92,918/61, p. 83.*

Lowenstein et al. A74,481/43: In rats, pretreatment with DOC increased, whereas thyroid feeding decreased, resistance to KCl i.p.

Pralidoxime ← cf. also *Table 104*

Selye G70,435/70: In rats, pralidoxime intoxication was counteracted by prednisolone and, to a lesser extent, by ethylestrenol and estradiol. CS-1, spironolactone, norbolethone, oxandrolone, progesterone, triamcinolone, DOC, hydroxydione, and thyroxine had no significant effect.

Propionitrile ← cf. also *Table 105*

Gellhorn 16,839/23: In mice, resistance against acetonitrile can be increased not only by thyroid extract but, to a lesser extent, also by extracts of various other tissues. These preparations also augment resistance to potassium cyanide (KCN) and propionitrile, whereas thyroidectomy and orchidectomy have an opposite effect.

Puromycin Aminonucleoside ←

Alexander & Hunt D20,284/61: In rats, pretreatment with T₃ aggravates the proteinuria caused by puromycin aminonucleoside.

Pyruvate ←

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram) are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Quinine ←

Karásek B52,652/37: In guinea pigs pretreated with thyroid extract or thyroxine, the isolated right auricles of the heart exhibit an accelerated pulse. In this respect quinine exerts an antagonistic effect.

Reserpine ←

Ershoff C60,006/58: In rats, reserpine and thyroid extracts, given in well-tolerated amounts, caused 100% mortality when administered concurrently.

Thier & Gravenstein C83,115/60: In isolated atria of rats, the slowing of the heart beat produced by reserpine is antagonized by thyroxine pretreatment *in vivo*.

Winter G71,836/65; F64,465/66;

F98,019/68: In mice, pretreatment with thyroid extract p.o. increases the toxicity of reserpine, chlordiazepoxide, imipramine and amphetamine.

Ashford & Ross H2,686/68: In mice, pretreatment with thyroid extract increased the toxicity of imipramine, nortriptyline, chlorpromazine, perphenazine and chlordiazepoxide, whereas the toxicity of meprobamate and reserpine was not enhanced.

Salicylates ←

Pfeiffer 16,694/23: In guinea pigs, thyroidectomy aggravates the drop in body temperature produced by cooling or salicylate injection i.p.

Vunder & Lapshina D34,912/56: In rats, mice and chickens, the goitrogenic effect of paraamino-salicylic acid is prevented by concurrent administration of thyroid extract.

Semicarbazide ←

Hunt & Carlton F3,186/64: In Pekin ducks, combined administration of semicarbazide and isoniazid p.o. produce a neurolathyrism-like syndrome which is not significantly influenced either by thiouracil or by DL-thyroxine.

SKF 525-A ← cf. *Table 106*

Sodium Chloride ←

Fregly C77,939/59: In rats, the hypertension induced by substitution of hypertonic NaCl for drinking fluid, as well as the accompanying cardiac and renal hypertrophy, are prevented by propylthiouracil.

Strychnine ← cf. also *Table 107*

Hunt & Seidell 50,346/09: In mice, pretreatment with thyroid extract does not influence resistance to strychnine.

Bálint & Molnár 34,586/11: In guinea pigs, the fatal effect of strychnine intoxication is inhibited by epinephrine or thyroid extract i.p.

Marañón & Aznar 46,926/11: In frogs, the fatal convulsions produced by strychnine can be prevented if, prior to injection, the drug is mixed with extracts of the posterior pituitary, the thyroid, various other tissues, and particularly epinephrine. [The possibility of delayed absorption owing to local vasoconstriction has not been considered (H.S.).]

Parhon & Urechia 62,361/13: In dogs and rabbits, orchidectomy and thyroidectomy do not influence resistance to strychnine consistently, but thyroid feeding appears to aggravate the characteristic convulsions.

Sulfa Drugs ←

Lehr & Martin C13,119/56: In rats, the production of cardiovascular lesions by "standard renal injury" (due to treatment with sulfa drugs) is prevented by thyroparathyroidectomy but not by thyroidectomy with parathyroid extract treatment. Curiously, "chemical thyroidectomy" [technique not specified (H.S.)] also inhibited, and thyroid hormone excess aggravated these lesions.

Lehr & Martin C23,011/56: In rats, the cardiovascular lesions produced by sodium acetylsulfathiazole (as a consequence of renal injury) are prevented by thyroparathyroidectomy, presumably because in the final analysis the changes observed are due to nephrogenic hyperparathyroidism.

Taurochenodeoxycholate ← Thyroxine: Voigt et al. H25,247/70

Tetrahydronaphthylamine ←

Borchardt 23,683/28: In cats, neither thyroparathyroidectomy nor adrenalectomy prevents the production of fever by tetrahydronaphthylamine, whereas denervation of the liver inhibits it almost completely.

Glaubach & Pick 11,431/30: In rabbits, the fever normally produced by tetrahydro- β -naphthylamine or cocaine is increased to fatal levels following pretreatment with thyroxine.

Thallium ←

Buschke 4,823/33; Buschke et al. 43,284/33: In mice, thyroxine increases, whereas thymus

extract decreases, sensitivity to thallium intoxication.

Uspenskaya D34,628/39: In rabbits, thallium intoxication is aggravated by chronic pretreatment with thyroid extract but not significantly influenced by thyroidectomy.

Theobromine ← cf. Table 108

Theophylline ← cf. also Table 109

Strubelt et al. G78,572/70: In rats, T3 increases, whereas thyroidectomy decreases, the calorogenic response to theophylline and caffeine, probably because the thyroid hormone activates adenylyl cyclase and/or inhibits phosphodiesterase.

Thimerosal ← cf. Table 110

Thioacetamide ←

Srinivasan & Balwani G64,503/68: In rats, pretreatment with thyroxine increased the liver damage produced by subsequent administration of CCl_4 or thioacetamide.

Thiourea ←

MacKenzie & MacKenzie A49,024/43: In rats, thyroidectomy offers no protection against the production of pulmonary edema by acute thiourea-overdosage.

Glock B23,056/45: In rats given normally fatal doses of thiourea, treatment with adrenocortical extract plus NaCl offers greater protection than NaCl alone. Thyroxine is a still more effective prophylactic even when given without NaCl.

Wiberg et al. E23,265/63: The mouse anoxia test performed after thiouracil treatment permits simultaneous assessment of survival and goitre prevention. The antigoitrogenic assay is more sensitive and permits greater precision than the anoxia test in the bioassay of thyroactive materials.

Tribromoethanol ← cf. also Table 111

Pribram A47,677/29: Both in rabbits and in man, single i.v. injections of thyroxine a few hours prior to administration of tribromoethanol diminish the actions of the latter.

Rutsch 7,744/33: In guinea pigs, thyroidectomy decreases, whereas thyroxine pretreatment increases, resistance to ether, para-dehyde or tribromoethanol anesthesia. These findings are ascribed to changes in the responsiveness of the brain.

Trichlorethanol ← cf. Table 112

Tri-o-cresyl phosphate ← cf. Table 113

Triton ←

Michel & Truchot C79,107/59: In thyroidec-tomized rats, the hypercholesterolemia and, to a lesser extent, perhaps also the cholesterol accumulation in the liver produced by triton WR-1339 are diminished by thyroxine.

Tryptophan ←

Bavetta et al. C47,327/57: In rats, various manifestations of tryptophan deficiency are aggravated by thyroid feeding.

D-Tubocurarine ← cf. Table 114

Tyramine ← cf. Table 115

Tyrosine ← cf. also Table 116

Schweizer B3,047/47: Addition of excessive amounts of L-tyrosine to the diet produces alkapturia, keratitis, conjunctivitis, alopecia, and inflammation of the paws in young rats. Among older animals, males are more sensitive than females. The severity of the syndrome is aggravated by thyroxine and inhibited by thiouracil.

Moore G36,616/65: In mice, pretreatment with T3 greatly increases sensitivity to the lethal effect of amphetamine. "Chlorpromazine, phenoxybenzamine, and propranolol pretreatment reduced the lethality of d-amphetamine in hyperthyroid mice while α -methyl-m-tyrosine, α -methyl-p-tyrosine, and reserpine pretreatment did not. The toxicity of α -methyl-m-tyrosine was enhanced in hyperthyroid mice."

Boctor et al. H22,509/70: In rats, tyrosine intoxication was aggravated by thyroxine and alleviated by thiouracil. "Plasma tyrosine concentration and liver tyrosine transaminase activity were high in rats fed a high tyrosine diet; thyroxine administration increased them further, but depressed slightly the activity of liver p-hydroxyphenylpyruvate hydroxylase."

Uranium ←

Rabboni & Milazzo B18,975/47: In rabbits, thyroidectomy protects against the production of toxic nephritis by conjoint administration of uranium acetate and epinephrine.

Vitamin A ←

Euler & Klussmann 4,928/32: In rats, the toxicity of thyroxine is partly inhibited by carotene and the authors suggest that perhaps "thyroxine is bound to carotene and thereby

inactivated." There may exist a physiologic antagonism between vitamin A and thyroxine.

Fasold & Heidemann 16,518/33: A goat normally excreted vitamin A but no carotene in its milk. After thyroidectomy, the milk of the same animal contained carotene but no vitamin A. It is assumed that thyroid hormone participates in the synthesis of vitamin A.

Abelin 57,019/33: In guinea pigs, thyroxine inhibits the hepatic storage of carotene and its transformation into vitamin A. In vitro studies suggest an actual chemical interaction between carotene and thyroxine.

Fasold & Peters A 54,337/33: In rats, hypervitaminosis A can be prevented by thyroxine. The hormone causes a resumption of growth and of carotene deposition in the liver.

Schneider & Widmann 33,725/35: In guinea pigs, both thyroidectomy and treatment with TTH considerably alter vitamin-A metabolism.

Fleischmann & Kann 67,360/36: In mice, vitamin A antagonizes the protective effect of thyroxine against acetonitrile intoxication. Vitamin A also antagonizes the effect of thyroxine upon tadpole metamorphosis. The enhancement of fatty acid oxidation by carotene in vitro is inhibited by thyroxine.

Greaves & Schmidt A 48,725/36: In rats, laparotomy and various toxic agents failed to influence vitamin-A requirements but these are increased by thyroxine or desiccated thyroid and decreased by thyroidectomy.

Sure & Buchanan A 48,611/37: In rats kept on specified diets, thiamine antagonizes the toxic actions of thyroxine but, at the same time, tends to increase vitamin-A requirements as manifested by the onset of xerophthalmia.

Logaras & Drummond A 16,392/38: Metabolic studies on rats kept on a vitamin-A-deficient diet "do not support the view that thyroxine increases the utilization or decreases storage of vitamin A."

Wohl & Feldman A 30,107/39: In patients with hyperthyroidism or hypothyroidism, dark adaptation is frequently deranged suggesting the existence of a disturbance in vitamin-A metabolism.

Baumann & Moore C38,599/39: In rats given an excess of vitamin A, thyroxine promoted catabolism and shortened survival. Earlier literature on an alleged antagonism between thyroxine and vitamin A is reviewed.

Canadell & Valdecasas B25,697/47: In rats kept on a vitamin-A deficient diet the characteristic trophic changes can be prevented by the administration of carotene. Thiourea blocks the protective effect of the provitamin A and the

effect of the antithyroid compound is in turn blocked by thyroid powder or iodine. The action of thiouracil is ascribed to the inhibition of carotenase activity.

Wiese et al. B39,257/48: In rats, thiouracil prolongs survival on vitamin-A deficient diets.

Woollam & Millen C64,432/58: The offspring of rats given large doses of vitamin A during pregnancy often show deformities of the skull and brain. This teratogenic effect is potentiated by methylthiouracil administration to the pregnant mother.

Nicol & Grangaud D20,176/61: In rats, thiouracil ameliorates the manifestations of vitamin-A deficiency. Progesterone has a similar effect.

Anderson et al. G11,709/64: In rats kept on diets with varying vitamin-A contents, the hepatic storage of vitamin A was increased by thyroxine as compared to thiouracil-treated controls, but the total vitamin-A storage of the body remained unaffected.

Khogali F73,238/66: In rats, hypervitaminosis A is aggravated both by L- and by D-triiodothyronine.

Sundaresan et al. G50,127/67: The vitamin-A requirements of rats are greatly increased during exposure to cold; this increase is abolished by thiouracil.

Vitamin-B Complex ←

Cameron & Moore 57,815/21: In pigeons kept on polished rice, wasting and death were accelerated by thyroid feeding but it is dubious whether this was true also of the specific manifestations of polyneuritis.

Nishimura & Nitta 1,171/29: In vitamin B complex deficient rats, thyroid feeding aggravates the severity of the resulting skeletal lesions.

Templeton & Patras 9,640/33: In rats, survival on a thiamine-deficient diet is prolonged by thyroparathyroidectomy but not significantly altered by desiccated thyroid.

Perelmutter & Miletzkaia 78,650/34: In pigeons on a B-avitaminotic diet, thyroid feeding accelerates the development of polyneuritis.

Sure & Buchanan A6,259/37: In rats, the loss of weight produced by thyroxine can be combated by thiamine.

Sure & Buchanan A48,611/37: In rats kept on specified diets, thiamine antagonizes the toxic actions of thyroxine but, at the same time, tends to increase vitamin-A require-

ments as manifested by the onset of xerophthalmia.

Infante et al. C17,520/55: In rats, vitamin-B₁₂ possesses no lipotropic potency in itself but does prevent hepatic steatosis on hypolipotropic diets supplemented with thyroxine.

Gershoff et al. C54,255/58: In rats, thyroxine greatly increases vitamin-B₁₂ requirements.

Vitamin C ←

Mouriquand & Michel 12,231/21: In guinea pigs kept on a normally adequate diet, scurvy-like bone changes developed upon treatment with thyroid extract. Other manifestations of scurvy have not been noted.

Abderhalden 13,399/23: In guinea pigs on an ascorbic acid-deficient diet, thyroidectomy aggravates but does not accelerate the development of scorbutic lesions.

Svirbely 33,140/35: In guinea pigs fed a vitamin-C deficient diet, the development of scurvy is accelerated by thyroid feeding.

Ganguli et al. G71,669/56: Chlorobutanol increases ascorbic acid synthesis and this effect can be suppressed by simultaneous administration of thyroxine, ATP, or malic acid.

McGraw C68,484/59; C80,136/59: Doctor's thesis describing numerous experiments on the effect of adrenalectomy, cortisone, thyroxine, thyroidectomy, thioureas and STH upon scorbutic guinea pigs, with special emphasis upon changes in capillary resistance and cold tolerance.

Vitamin D, DHT ← cf. also Selye G60,083/70, p. 400.

Kunde & Williams 18,960/27: In rats thyroidectomized (without removing the parathyroids) 15—29 days after birth, even very large amounts of cod liver oil cannot prevent the development of rickets on a rachitogenic diet.

Schechet B61,419/51: In rats, addition of desiccated thyroid or iodinated casein to a rachitogenic diet assures more regular growth and thereby facilitates the bioassay of vitamin-D preparations.

Gillman & Gilbert C31,076/56: The arterial lesions produced by heavy vitamin-D overdosage in the rat are aggravated by thyroxine or DOC, whereas cortisone and thyroidectomy offer considerable protection.

Selye C27,735/57: The cardiovascular calcification and nephrocalcinosis produced by DHT in rats are aggravated by estradiol,

cortisol, ACTH and thyroxine. Conversely, methyltestosterone and STH exert a protective effect.

Takens C69,439/59: In rabbits, the calcinosis and other toxic manifestations of vitamin-D₂ overdosage are accentuated by pretreatment with methylthiouracil.

Manston G69,733/69: The metastatic calcification produced by vitamin-D₃ overdosage in the cow can be prevented by thyroxine.

DHT ← cf. also Table 117

Vitamin E ←

Wheeler & Perkins B43,572/49: In chicks, vitamin-E requirements are increased by pretreatment with thyroprotein and decreased by thiouracil.

Tentori et al. C7,904/54: In rats, thyroid feeding accelerates the development of the characteristic skeletal muscle lesions produced by vitamin-E deficiency.

Fudema et al. D23,102/62: In rabbits, the muscular dystrophy and death induced by vitamin-E deficiency are delayed following suppression of thyroid activity by ¹³¹I.

Vitamins (Pantothenic Acid) ←

Haque et al. B19,204/48: In chicks fed a ration low in folic acid and pantothenic acid, thyroxine caused high mortality but the pantothenic acid-deficiency symptoms were partially counteracted. Review of the literature.

W-1372 ← cf. Table 118

Water ←

Gaunt 84,566/44: Rats are protected against water intoxication by thyroxine. This effect is largely abolished by adrenalectomy.

Zoxazolamine ← cf. also Table 119

Conney & Garren D78,956/60: In rats, pretreatment with thyroxine i.p. shortened the

duration of action of zoxazolamine by increasing its metabolism in vivo. However, thyroxine unlike phenobarbital and other drugs did not accelerate zoxazolamine metabolism by increasing the activity of hepatic microsomal enzymes; the shortening of zoxazolamine action by thyroxine was correlated with increased activity of glucose-6-phosphate and 6-phosphogluconate dehydrogenases which are involved in the generation of NADPH.

Conney & Garren D93,666/61: In rats, thyroxine shortens the duration of action of zoxazolamine by accelerating its metabolism through hepatic microsomes.

Harbison & Becker H10,917/69: Thyroidectomy greatly prolonged hexobarbital sleeping time and zoxazolamine paralysis in rats. T3 increased the response to hexobarbital but decreased the effect of zoxazolamine. The mortality rates induced by high doses of hexobarbital, thiopental, amobarbital, pentobarbital and phenobarbital were all significantly increased in rats pretreated with T3.

Zoxazolamine ← **Thyroxine**: Conney et al. D93,666/61*

Varia ←

Hunt & Seidell 50,346/09: Systematic studies on the effect of thyroid extract upon the resistance of mice to a great variety of toxic substances.

Störtebecker 76,398/39: Review of the early literature on the effect of thyroid hormone upon resistance to various drugs.

Selye G70,480/71: In rats, pretreatment with thyroxine diminished resistance to intoxication with dioxathion and parathion. It failed to affect poisoning with digitoxin, nicotine, hexobarbital, progesterone (anesthesia), zoxazolamine, indomethacin, acute DHT induced tissue calcinosis or the infarctoid myocardial necroses produced by fluorocortisol + Na₂HPO₄ + corn oil.

Complex Diets ←

In rabbits, thyroidectomy moderately decreases the catabolic effect of fasting. Thyroid feeding accelerates catabolism in rats kept on vitamin-free diets.

Nutritional hepatic cirrhosis (such as is seen on various hypolipotropic diets) is prevented by propylthiouracil and other thioureas in proportion to their goitrogenic effect, whereas thyroid feeding has an opposite action.

In hamsters, gallstone formation on a diet containing 24% rice starch is increased by concurrent treatment with thyroxine.

Blum 38,401/00; 38,405/06: Studies on the effect of thyroidectomy upon the resistance of dogs, rabbits, and sheep to feeding various diets led to the conclusion that the thyroid is not an organ of internal secretion but acts by accumulating and destroying endogenous toxic substances especially those derived from meat diets.

Mansfeld & Müller 35,416/11: In rabbits, thyroidectomy inhibits the protein catabolic effect of exposure to decreased oxygen tension, hydrocyanic acid intoxication or fasting.

Hari 51,049/19: Contrary to earlier claims, even thyroidectomized rabbits show intense protein catabolism during fasting.

Cameron & Moore 57,815/21: In rats kept on a vitamin-free diet (oatmeal and water), thyroid feeding produced a particularly rapid loss of weight.

György et al. G71,701/48: In rats, hepatic cirrhosis produced by a complex hepatotoxic diet is prevented by propylthiouracil and other thioureas in proportion to their goitrogenic effect.

Sellers & You B68,641/51: In rats kept on a choline-deficient diet, propylthiouracil retards

the development of hepatic cirrhosis and fatty cyst formation; thyroid feeding has an opposite effect.

Dryden & Hartman C66,416/59: In rats kept on various complex diets during treatment with thyroprotein, no single nutrient could be found which would antagonize the manifestations of hyperthyroidism.

Bergman & van der Linden G30,642/65: In hamsters, gallstone formation on a diet containing 24% rice starch, is increased by concurrent treatment with D-thyroxine. At the same time, the animals develop fatty livers. On a diet containing 72.3% rice starch, the gallstone-forming action of D-thyroxine is blocked although hepatic steatosis still occurs.

Bergman & van der Linden G43,913/66; G39,200/66: In hamsters kept on certain diets, thyroxine promotes gallstone formation. Cholestyramine prevents this effect.

Borgman & Haselden H29,947/70: In rabbits kept on a gallstone producing ration, ACTH, thyroid hormones or cortisone did not inhibit the production of biliary calculi, but several of these hormones inhibited the usually associated hepatic steatosis.

Microorganisms, Parasites and Their Products ←

Bacteria and Vaccines ←. Numerous investigations dealt with the effect of thyroid hormones upon the course of various bacterial infections but special attention was given in this connection to tuberculosis. In guinea pigs, thyroidectomy and thiouracil diminish, whereas thyroxine and T3 increase, resistance to tuberculosis. Essentially similar observations were made in rabbits and in mice. However, in the latter species, pretreatment with thyroxine or dinitrophenol in doses sufficient to limit the weight gain of noninfected controls, diminished resistance to infection with tuberculosis.

Heavy overdosage with thyroxine also diminishes resistance to various other bacterial infections (e.g., plague bacilli, *S. typhi*, *staphylococcus*, *streptococcus*) although it increases resistance to some infections (e.g., chicken cholera); we have no valid explanation for this dual effect although it may be due to incidental conditioning factors (dosage, timing, diet, etc.) as much as to the type of microbe used.

Viruses ←. In monkeys, resistance to poliomyelitis virus is allegedly not affected either by thyroidectomy or by thyroxine, but in mice, it is increased by thyroid extract and decreased by thiouracil.

In rats, sensitivity to various strains of encephalitis virus is augmented by thyroxine and the same appears to be the case in mice vaccinated and subsequently infected with influenza.

Parasites ←. Thyroid feeding has an adverse effect upon mice infected with *Hymenolepis* tapeworms, whereas thiouracil increases resistance to these parasites.

In chickens, thiouracil did not appear to alter resistance to cecal coccidiosis (*Eimeria tenella*) significantly but mild hyperthyroidism, induced by thyroactive

iodocasein, increased the ability of chicks to overcome infection with *Ascaridia galli* or *Heterakis gallinae*.

Allegedly thyroidectomy or pretreatment with thioureas also slightly decreases resistance to toxoplasma and to *Trichinella spiralis* in the mouse.

Bacterial Toxins ←. In guinea pigs and rabbits, thyroidectomy or treatment with thyroid preparations produced only minor and variable changes in resistance to various endotoxins. Allegedly, in mice, the lethal action of endotoxins is enhanced by T3 or thyroxine, whereas in guinea pigs thyroxine diminishes the lethal effect of tetanus toxin.

Bacteria and Vaccines ←

Bacillus Anthracis ←. *Weinstein B15,029/39:* In mice, various anterior pituitary preparations protect against infection with *B. anthracis*. Parathyroid extract was also very effective, whereas thyroxine and testosterone offered little protection and progesterone, insulin, "estrin" and posterior lobe extract were virtually ineffective.

Brucella Melitensis ←. *Bradley & Spink C76,042/59:* In mice, infected with small numbers of *B. melitensis*, hepatic granulomas occurred without necrosis. Severe necrosis developed after pretreatment with T3 without multiplication of brucellae and with minimum inflammatory lesions. Necrosis was not induced by T3 in mice given brucella endotoxin after T3 treatment.

Klebsiella Pneumoniae ←. *Martin & Bullard H15,263/69:* In mice, resistance to infection by *K. pneumoniae* is increased by propylthiouracil and decreased by thyroxine.

Mycobacterium Tuberculosis ←.

GUINEA PIG

Kepinow & Metalnikow 40,285/22: Thyroidectomized guinea pigs infected with tubercle bacilli do not respond with fever to a subsequent tuberculin injection although their survival rate is not altered.

Izzo & Cicardo B23,261/47; B67,482/47: In guinea pigs, thyroidectomy diminishes, whereas thyroxine increases, resistance to infection with tubercle bacilli. The clinical literature on the effect of hyperthyroidism upon tuberculosis is reviewed.

Swedberg B59,988/51: Thyroxine diminishes the resistance of guinea pigs to tuberculosis. "Estrogen" has the same effect, whereas testosterone does not significantly change the course of the infection.

Wasz-Höckert et al. C30,699/56: In guinea pigs, methylthiouracil aggravated, whereas

thyroid extract ameliorated, the course of experimental tuberculosis.

Renovanz C78,772/59: In guinea pigs, the course of experimental tuberculosis was not markedly influenced by ACTH, tolbutamide derivatives or antithyroid treatment with perchlorates.

Solanki & Junnarkar D21,370/61: In guinea pigs, pretreatment with thyroxine increases the resistance to tuberculosis by augmenting the phagocytic capacity of mono-nuclear leukocytes.

Bloch D61,174/63: In guinea pigs, resistance to tuberculosis is increased by T3.

Vakilzadeh & Vandiviere E32,626/63: In guinea pigs, the beneficial effect of vaccination against tuberculosis was greatly increased by thyroxine and T3, but not by cortisone, cortisol or ACTH. None of the hormones altered natural host resistance in nonimmunized guinea pigs.

RABBIT

Lurie & Ninos C14,387/56: In rabbits pretreatment with T3 inhibits, whereas thiouracil aggravates, the course of experimental tuberculosis.

Lurie et al. C14,963/56; C52,055/58: In rabbits, the course of pulmonary tuberculosis is ameliorated by treatment with T3 or thyroxine and aggravated by propylthiouracil or thyroidectomy. Dinitrophenol exerts no conspicuous effect.

Lurie et al. C64,295/59: In rabbits, thyroidectomy or propylthiouracil reduced the native resistance to human tubercle bacilli. T3 exerted no consistent effect upon tuberculin sensitivity but greatly inhibited the growth of bacilli and enhanced resistance to infection.

Lurie et al. C65,610/59: Various strains of inbred rabbits were infected with tuberculosis bacilli. "Hyperthyroidism induced by L-triiodothyronine or L-thyroxine suppressed to a greater or lesser degree the inception and

progress of the pulmonary tuberculosis produced by the quantitative inhalation of human tubercle bacilli in four races, AD, III, IIIC, CaC, and IIIA, with low or intermediate genetic resistance to the disease. L-Triiodothyronine also exerted a definite suppressive influence on the development of an already existing tuberculosis when the hormone was administered three weeks after the infection."

Dzyubinskaya C97,348/60: Pretreatment with methylthiouracil aggravates the course of experimental tuberculosis in rabbits.

MOUSE

Dubos D93,317/55; G71,484/55: In mice, resistance to tuberculosis is decreased by pretreatment with thyroxine or dinitrophenol p.o. in amounts sufficient to limit the weight gain of noninfected controls. These findings, as well as observations on dietary factors influencing resistance to tuberculosis, led to "the hypothesis that a decrease in resistance to infection can be brought about by metabolic disturbances which cause either a depletion of the glycogen reserves of the body, or a reduction in the glycolytic activity of inflammatory cells, or an increase in the concentration of certain polycarboxylic acids and ketones in the tissues."

Maśliński C50,519/56: In mice, the histologic reaction to infection with tuberculosis is somewhat altered by pretreatment with "thyroid hormone" or methylthiouracil, but survival is not significantly changed.

Maśliński C50,520/56: In mice, severe overdosage with methylthiouracil or desiccated thyroid aggravates the course of tuberculosis. There is, however, an optimum state of hyperthyroidism in which the intensity of the tuberculous changes is the lowest.

Chirico et al. C67,012/59: In mice, small doses of thyroxine diminish mortality and prolong the mean survival time following infection with tubercle bacilli.

Backman C94,674/60: In mice, both methylthiouracil and desiccated thyroid aggravate the course of experimental tuberculosis.

RAT

Steinbach 92,528/32: In rats, parathyroidectomy lowers resistance to infection with bovine but not with human tuberculosis. Thyroparathyroidectomy makes rats susceptible to both human and bovine tubercle bacilli.

VARIA

Schäfer B99,955/54: Monograph (127 pp., numerous refs.) on the role of endocrine factors in tuberculosis. Special sections are devoted to the hormones of the thyroid, parathyroid, thymus, adrenals, pancreas and gonads.

Maśliński C48,845/57: Review (55 pp., 114 refs.) on the relationship between tuberculosis and the thyroid. Personal observations on mice revealed that following infection with tuberculosis mortality was increased by methylthiouracil in comparison with controls receiving thyroid preparations or no hormone treatment.

Debry et al. D34,828/62: Review (14 pp., 64 refs.) on the relationship between tuberculosis and thyroid activity.

Mycoplasma ←. Tripi et al. B12,732/49: In rats, the production of polyarthritis by PPLLO organisms was enhanced and the mortality increased following chronic pretreatment with thiouracil. Thyroidectomy (inducing a similar or greater drop in BMR) did not change this form of polyarthritis. Presumably, thiouracil acts "through some peculiar intrinsic action" rather than by merely diminishing thyroid activity.

Pasteurella ←. Marbé 34,321/10: In guinea pigs, pretreatment with thyroid extract diminishes resistance to infection with plague bacilli and counteracts the protective effect of antiplague serum.

Parhon & Parhon 36,340/14: During a chicken cholera epidemic, a small number of thyroid extract-treated chickens survived better than controls.

Salmonella Typhi ←. Marbé 34,320/10; A23,018/10: In guinea pigs, resistance to infection with typhoid bacilli is diminished by pretreatment with thyroid extract.

Marbé A23,015/12: Addition of thyroid extract to cultures of typhimurium bacilli in vitro increases their virulence.

Shigella ←. Melnik 26,134/25: In rabbits, thyroidectomy offers some protection against infection with Shiga bacilli.

Staphylococcus ←. Lauber 9,102/32: Observations on the effect of vasopressin, epinephrine, thyroid extract and insulin upon streptococcal and staphylococcal infections in mice.

Sealy A56,716/42: In rabbits, desiccated thyroid does not produce liver necrosis in itself but facilitates its production after infection by *S. aureus*. A review of the literature also suggests that uncomplicated hyperthyroidism does not result in liver necrosis.

either in experimental animals or in man unless there is a complicating infection.

Dubos et al. C21,520/55; Dubos G71,484/55: In mice, thyroxine pretreatment diminishes resistance to infection with *S. aureus*. The resistance-diminishing effect of thyroxine and dinitrophenol against other infections is briefly mentioned.

Smith & Dubos C12,130/56: In mice, pretreatment with thyroid extract or dinitrophenol decreases resistance to staphylococcal infection.

Hedwall & Heeg D14,804/61: In rats, an experimental staphylococcus pyelonephritis is aggravated by pretreatment with thyroxine.

Streptococcus ←. Lauber 9,102/32: Observations on the effect of vasopressin, epinephrine, thyroid extract and insulin upon streptococcal and staphylococcal infections in mice.

Schultz 99,001/38: In guinea pigs and rabbits, pretreatment with thyroxine increases susceptibility to the development of purulent myocarditis after s.c. inoculation with hemolytic streptococci.

Varia ←. Marbé A4,623/08; A4,624/08; A4,625/08; A4,626/09; A4,627/09; A23,010/09; A23,011/09; A23,012/09; A23,013/09; A23,016/10; 34, 561/10: Studies on the effect of thyroidectomy and thyroid extract upon opsonin formation and phagocytosis of bacteria in guinea pigs and rabbits.

Murphy et al. C60,008/58: In mice, resistance to infection with *C. albicans* or *S. pyrogens* is increased by pretreatment with T3 but this hormone does not significantly alter resistance to transplanted leukemia.

Nutter et al. C65,285/59: In mice, T3 decreases survival time after infection with tubercle bacilli or pneumococci.

Viruses ←

Levaditi & Haber 33,069/35: In Macacus cynomolgus monkeys, resistance to poliomyelitis virus, acquired by prior infection, is not influenced by thyroidectomy, orchidectomy or thyroxine administration.

Holtzman B1,287/46: In mice, resistance to infection with polio virus is increased by thyroid extract and decreased by thiouracil. The comparative polio resistance of mice kept in a cool environment may be secondary to increased thyroid hormone production.

Hurst et al. C94,089/60: Cortisone, ACTH, estradiol, stilbestrol and thyroxine all stimulate the growth of the virus of equine encephalomyelitis in the dog whereas testosterone and

progesterone do not. The hormones which aggravate the infection also counteract the prophylactic effect of mepacrine and abolish the normally greater resistance of the females.

Jandásek C88,870/60: In suckling rats infected with tick encephalitis survival was greatly shortened by thyroxine. Neither antibody production nor the number of virus carriers was influenced by the hormone.

Jandásek C92,117/60: Mice become particularly sensitive to infection by encephalitis virus (strain Hypr) following pretreatment with thyroxine.

Lungu et al. F84,406/67: In mice vaccinated against influenza, subsequent infection with the virus causes an increased mortality following treatment with thyroxine or thiouracil.

Jannuzzi et al. H27,335/70: In patients with viral hepatitis, various anabolics, including stanozolol and 4-chlorotestosterone, exert a beneficial effect.

Parasites ←

Larsh Jr. A47,571/47: In old mice, thyroid feeding has an adverse effect on infestation with *Hymenolepis* tapeworms, whereas thiouracil increases resistance to the parasites. In young mice, the infestation was much less dependent upon the thyroid status.

Wheeler et al. A48,602/48: In chickens, a preliminary study suggests that thiouracil-induced hypothyroidism does not significantly affect resistance to cecal coccidiosis induced by infection with *Eimeria tenella*.

Todd G71,890/48: In chickens infected with *Ascardia galli* or *Heterakis gallinae*, mild hyperthyroidism induced by feeding thyroactive iodocasein (Protamone) increased the ability of the birds to overcome the worm infestation. Thiouracil had a detrimental effect.

Todd B40,185/49: In chickens infected with *Ascardia galli* or *Heterakis gallinae*, treatment with thyroactive iodocasein or thiouracil caused no significant difference in the development of either worm; however, "specimens of *H. gallinae* attained significantly greater lengths in mildly hypothyroid birds."

Hirschlerowa C35,235/56: Thyroidectomy or pretreatment with methylthiouracil decreases resistance to infection with toxoplasma unless the animals are given substitution therapy with thyroid extract.

Krupa et al. G45,694/67: In mice, propylthiouracil slightly decreased resistance to infestation with *Trichinella spiralis* larvae but the results were not consistent.

Bacterial Toxins ←

Marbé 35,374/11: In guinea pigs, thyroid feeding increases sensitivity to diphtheria toxin.

Hari 40,209/21: Polemic remarks concerning the technique and interpretation of earlier data on the effect of thyroidectomy upon the resistance to cyanides, chloroform, bacterial toxins and oxygen deficiency.

Houssay & Sordelli A 48,113/21: In rabbits, thyroidectomy does not change sensitivity to diphtheria toxin. In guinea pigs, sensitivity to diphtheria toxin, tetanus toxin and to cobra venom is likewise not modified by removal of the thyroid.

Locatelli 28,678/34: In dogs, thyroidectomy diminishes the wave of mitosis in hepatocytes normally produced by small doses of diphtheria toxin.

Sealy & Lyons B 46,719/49: In rabbits, sterile inflammation produced by staphylococcus toxin s.c. causes hepatic necrosis if the animals are pretreated with thyroid extract.

Kroneberg & Pötzsch E 54,858/52: In mice, thyroxine pretreatment increases sensitivity to endotoxin.

Melby et al. C 86,232/58: In mice, T3 increases the lethal effect of *Br. melitensis* endotoxin. In mice infected with *Br. melitensis*, unique hepatic lesions develop under the influence of T3 pretreatment which are not seen in unpretreated controls.

Bradley & Spink C 76,042/59: In mice, infected with small numbers of *Brucella*

melitensis, hepatic granulomas occurred without necrosis. Severe necrosis developed after pretreatment with T3 without multiplication of brucellae and with minimum inflammatory lesions. Necrosis was not induced by T3 in mice given *Brucella* endotoxin after T3 treatment.

Melby & Spink C 72,440/59: In mice, the lethal action of various endotoxins is enhanced by pretreatment with T3.

Gordon & Lipton C 94,649/60: 5-HT reduces endotoxin mortality in mice. This effect is greater in females than in males and is potentiated by cortisol. Thyroxine aggravates the toxicity of endotoxin.

Yokoi et al. D 8,839/61: In rabbits, a biphasic fever pattern is elicited by *Sh. flexneri* type 6 pyrogen. The biphasic nature of the response was maintained after thyroidectomy but largely abolished by adrenal demedullation.

Schoen & Voss D 11,906/61: In guinea pigs, the lethal effect of tetanus toxin is inhibited by pretreatment with thyroxine.

E-coli Endotoxin ← cf. also Table 123

Venoms ←

Houssay & Sordelli A 48,113/21: In rabbits, thyroidectomy does not change sensitivity to diphtheria toxin. In guinea pigs, sensitivity to diphtheria toxin, tetanus toxin and cobra venom is likewise not modified by removal of the thyroid.

Immune Reactions ←

Most of the studies on the effect of thyroid hormones upon immune reactions have been performed on guinea pigs which are notoriously sensitive to anaphylaxis.

The formation of various antibodies has been claimed to be inhibited by thyroidectomy and stimulated by thyroid extract. In sensitized guinea pigs, thyroid extract, administered a few days before a challenging dose of horse serum, protects against fatal anaphylactic shock. However, thyroidectomy prior to sensitization allegedly has the same effect, whereas this is not the case if the thyroid is removed after sensitization. Indeed, it has been claimed that, in guinea pigs, thyroidectomy blocks anaphylaxis unless the animals are treated with thyroid. Suppression of anaphylactic reactivity by anterior hypothalamic lesions can be partially overcome by thyroid hormones in guinea pigs.

Particularly extensive studies have been performed in guinea pigs concerning the role of the thyroid apparatus in the reaction to tuberculin. Moderate thyrotoxicosis produced by two weeks' pretreatment with thyroxine increases tuberculin hyper-

sensitivity. Propylthiouracil does not affect it, but the suppression of hypersensitivity by cortisone or ACTH is allegedly abolished by pretreatment with this goitrogen.

The beneficial effect of vaccination against tuberculosis is also increased in guinea pigs by thyroxine or T3.

If dogs are sensitized after thyroidectomy, subsequent anaphylactic shock is mild. Thyroidectomized dogs are also relatively insensitive to peptone shock. In rabbits, Masugi nephritis is considerably aggravated by pretreatment with thioureas.

Marbé A 4,623/08; A 4,624/08; A 4,625/08; A 4,627/09; A 4,626/09; A 23,010/09; A 23,011/09; A 23,012/09; A 23,013/09; A 23,016/10; 34,561/10: Studies on the effect of thyroidectomy and thyroid extract upon opsonin formation and phagocytosis of bacteria in guinea pigs and rabbits.

Müller A 47,855/11: In guinea pigs, the formation of various antibodies is inhibited by thyroidectomy as well as by surgical interference with hepatic circulation. Treatment with thyroid extract has an opposite effect. The latter is not due to shock, since removal of all abdominal organs except the liver is ineffective. Furthermore, the blood loses its "alexic power" when perfused through an isolated liver preparation.

Savini & Savini A 24,559/15: In sensitized guinea pigs, pretreatment with thyroid extracts a few days before administration of a challenging dose of horse serum protects against fatal anaphylactic shock.

Képinow 13,298/22: In guinea pigs, thyroidectomy blocks anaphylaxis unless they are treated with thyroid extract.

Képinow & Lanzenberg 13,258/22: Preliminary studies on the effect of thyroidectomy upon anaphylaxis and antibody formation in guinea pigs.

Lanzenberg & Képinow 13,117/22: In guinea pigs, thyroidectomy prior to sensitization prevents subsequent anaphylactic shock, whereas this is not the case if the thyroid is removed after sensitization.

Appelmans 14,085/23: Anaphylactic shock develops normally in thyroidectomized guinea pigs even if both the sensitizing and the challenging dose of antigen are administered after the operation.

Houssay & Sordelli 13,430/23: Comparative studies on the influence of thyroidectomy upon anaphylaxis in the guinea pig, rabbit and dog.

Képinow 13,941/23: Discussion of the optimal conditions for the prevention of anaphylaxis by thyroidectomy in guinea pigs.

Parhon & Ballif 13,548/23; 17,302/23: In guinea pigs, anaphylaxis is diminished after thyroidectomy but not significantly influenced by thymectomy.

Houssay & Cisneros 26,936/25: In dogs sensitized after thyroidectomy, subsequent anaphylactic shock is diminished. Thyroidectomized dogs are also comparatively insensitive to peptone shock.

Fleisher & Wilhelmj 23,337/27: In guinea pigs, thyroidectomy before sensitization diminishes the severity of subsequent anaphylactic shock. In rabbits, this inhibition is not clear-cut although there does appear to occur some change in the reaction of thyroidectomized rabbits following the second injection of antigens. Immunological studies suggest that thyroidectomy does not prevent the formation of antibodies but merely alters the reaction during shock.

Spinelli 7,369/32: In guinea pigs, thyroidectomy increases resistance to anaphylactic shock.

Long & Miles D 41,973/50: In guinea pigs, moderate thyrotoxicosis produced by two weeks' treatment with thyroxine increases hypersensitivity to tuberculin, whereas moderate doses of propylthiouracil do not affect it. ACTH and cortisone diminish tuberculin sensitivity. Fourteen days after stopping thyroxine injections, the animals became actually less hypersensitive than the controls. A similar reversal of effect was noted two weeks after interruption of cortisone or ACTH treatment in that the animals became more hypersensitive than the controls.

Strehler & Sollberger B 54,646/50: In rabbits, Masugi nephritis is greatly aggravated by pretreatment with tetramethylthiourea.

Long et al. B 60,189/51: In B.C.G.-infected guinea pigs, hypersensitivity to tuberculin is considerably diminished by cortisone or ACTH. This diminution is abolished by pretreatment with propylthiouracil, which alone has no effect upon hypersensitivity. Pre-

treatment with thyroxine increases tuberculin hypersensitivity but does not block the sensitization by ACTH or cortisone. Apparently, thyroxine is necessary for the desensitizing action of ACTH and cortisone.

Long et al. B63,843/51: In guinea pigs, dihydroascorbic acid—unlike ascorbic acid—inhibits the tuberculin reaction after infection with B.C.G. vaccine. The desensitizing effect of dihydroascorbic acid is not inhibited by thiouracil. Alloxan, like ACTH or cortisone, does not modify desensitization by ascorbic acid on diets deprived of the "cabbage factor"; it desensitizes guinea pigs on a cabbage diet and this desensitization is inhibited by pro-pylthiouracil.

Long & Shewell G71,833/54: In guinea pigs, allergic hypersensitivity to B.C.G. is increased by thyroxine or insulin. Partial pancreatectomy has no effect on sensitivity by itself but prevents the action of thyroxine, although not that of insulin.

Long & Shewell G71,832/55: In guinea pigs, thyroxine increases immunity as judged by the local response to diphtheria toxin injected intradermally and of circulating anti-toxin after immunization with diphtheria toxoid. Partial pancreatectomy prevents this effect of thyroxine.

Long C32,348/57: In guinea pigs, both anaphylactic shock (horse serum) and sensitiv-

ity to histamine are greatly increased by pre-treatment with thyroxine. Thyroxine also augments the sensitivity of guinea pigs to intradermal tuberculin injection.

Vakilzadeh & Vandiviere E32,626/63: In guinea pigs, the beneficial effect of vaccination against tuberculosis was greatly increased by thyroxine and T3, but not by cortisone, cortisol or ACTH. None of the hormones altered natural host resistance in nonimmunized guinea pigs.

Lupulescu et al. F77,999/66: In rabbits, the formation of antibodies against brucella S₆ is stimulated by thyroxine and 4-chlorotestosterone but decreased by thiourea. The effect of 4-chlorotestosterone is evident even after destruction of the thyroid and hence is not mediated through the latter gland.

Filipp & Mess G71,129/69: In guinea pigs, suppression of anaphylactic reactivity by anterior hypothalamic lesions can be partially blocked by chronic treatment with thyroid hormones as well as by adrenalectomy or adrenal inactivation by metyrapone (Metopirone). "Combined treatment of guinea pigs bearing hypothalamic lesions with Metopirone and thyroxine completely eliminated the blocking effect of the tuberal lesion on anaphylactic reactions." Apparently the shock-inhibiting effect of hypothalamic lesions is partly due to hypothyroidism and partly to hyperadrenalcorticoidism.

Special Surgical Interventions ←

Hepatic Lesions ←. In rats, desiccated thyroid feeding increases the weight of the liver under normal conditions and the rate of regeneration after partial hepatectomy. Curiously, thiouracil has also been claimed to accelerate liver regeneration under similar conditions but this was denied by several investigators, who found that even thyroidectomy had no significant effect upon the regeneration of hepatic tissue in the rat.

In dogs, the manifestations of shock produced by constriction of the hepatic veins were aggravated by thyroid feeding and constriction of the portal vein caused ascites only after pretreatment with methylthiouracil.

Ascites produced by subdiaphragmatic constriction of the inferior vena cava was inhibited by thyroidectomy and restored by a thyroid extract in one series of experiments. However, other investigators pointed out that subdiaphragmatic constriction of the inferior vena cava causes ascites in itself and that this can be ameliorated by thyroidectomy, though only if the operation is performed after the caval constriction.

Renal Lesions ←. In uninephrectomized rats, compensatory hypertrophy of the remaining kidney is diminished, but not prevented, by thyroidectomy. Regeneration is inhibited by thiouracil and enhanced by thyroxine under these conditions.

The pressor effect of renal encapsulation is diminished by methylthiouracil and increased by thyroxine in the rat. However, thyroidectomy performed after the kidneys had been encapsulated for 9-19 weeks has only a slight effect upon the blood pressure.

The metastatic calcification produced by complete nephrectomy in rats is uninfluenced by thyroxine although it can be prevented by calcitonin. Presumably, the previously described protective effect of thyroxine against exogenous parathyroid hormone depends upon the presence of the kidney.

In dogs and rats, destruction of the thyroid by radio-iodine increases survival after bilateral nephrectomy perhaps merely because general metabolism is greatly diminished.

Hepatic Lesions ←

Higgins 9,809/33: In rats, desiccated thyroid feeding increases the weight of the liver under normal conditions, and the rate of regeneration after partial hepatectomy.

Hepler & Simonds A15,174/38: In dogs, the manifestations of shock produced by constriction of the hepatic veins are aggravated following thyroid feeding.

Fogelman & Ivy B23,357/48: In rats, thiouracil accelerates liver regeneration after partial hepatectomy.

Drabkin B17,795/48: In rats, thyroidectomy moderately diminishes liver regeneration after partial hepatectomy and reduces cytochrome c in skeletal muscle, heart, liver and kidney.

Spigolon B52,689/49: In dogs, gradual constriction of the portal vein caused ascites only if the animals were pretreated with methylthiouracil.

Christensen & Jacobsen A49,204/49: In rats subjected to partial hepatectomy, neither hypophysectomy nor thyroidectomy impairs the rate of regeneration. No significant change in mitotic rate was observed after pretreatment with stilbestrol or STH.

Drabkin D18,388/50: In rats, thyroidectomy or thiouracil treatment does not significantly impair liver regeneration after partial hepatectomy, whereas thyroxine markedly inhibits it.

Giberti et al. B82,948/53: In rats, propylthiouracil does not inhibit liver regeneration after partial hepatectomy but prevents hepatic steatosis.

Weinbren D95,941/59: Review (11 pp., 110 refs.) and personal observations on factors influencing hepatic regeneration after partial hepatectomy in the rat, with special sections on the effects of hypophysectomy and thyroid hormones.

Canter et al. C67,855/59; Baronofsky & Canter C85,341/60: In dogs, the production of ascites by subdiaphragmatic constriction of the inferior vena cava is inhibited by thyroidectomy and restored by subsequent treatment with thyroid extract.

Poll et al. D4,775/61: In dogs, ascites produced by supradiaphragmatic constriction of the vena cava inferior is usually ameliorated by thyroidectomy, but only if the operation is performed after caval constriction.

Girkin & Kampschmidt C99,934/61: In rats, the hepatic enlargement induced by Walker tumor transplants or by partial hepatectomy is inhibited by thiouracil and largely restored by subsequent thyroxine treatment.

Renal Lesions ←

McQueen-Williams & Thompson A33,938/40: In rats, total hypophysectomy prevented the compensatory hypertrophy of the remaining kidney after uninephrectomy. Thyroidectomy did not prevent renal regeneration under identical conditions.

Zeekwer 84,592/44: In rats, thyroidectomy does not significantly alter renal regeneration following unilateral nephrectomy.

Herlant B30,957/47: In uninephrectomized rats, regeneration in the remaining kidney is inhibited by thiouracil.

Herlant B30,956/48: In uninephrectomized rats, thyroxine greatly increases the number of mitoses in the proximal tubules of the remaining kidney.

Valori B46,667/48: In rats, thyroidectomy diminishes but does not abolish compensatory hypertrophy of the remaining kidney after uninephrectomy.

Kleinsorg & Loeser B41,137/49: In rats, compensatory hypertrophy of the remaining kidney following uninephrectomy is enhanced by thyroxine and inhibited by methylthiouracil.

Bächtold *B*60,463/50: In rats, the pressor effect of renal encapsulation is diminished by pretreatment with methylthiouracil and increased by thyroxine.

Marshall & Freeman *B*68,239/52; *B*96,575/54: In dogs and rats, destruction of the thyroid by ^{131}I increases survival time after bilateral nephrectomy.

Braun-Menéndez *C*4,927/54: In rats, the hypertension produced by figure-of-8 ligature is diminished by thyroidectomy or thiouracil and increased by thyroid powder p.o.

Osipovich *C*58,570/57: In uninephrectomized rats, methylthiouracil enhances compensatory hypertrophy of the remaining kidney, presumably as a consequence of increased TTH secretion. The acceleration of compensatory renal hypertrophy by exposure to cold is ascribed to a similar mechanism.

Fregly et al. *C*66,042/59: In rats, the hypertension produced by bilateral renal encapsulation is prevented by thyroidectomy or propylthiouracil.

Fregly et al. *C*80,398/60: In rats, after renal encapsulation, propylthiouracil reduced the systolic blood pressure even more than did complete thyroidectomy. However, the cardiac hypertrophy of renal hypertension was not prevented by propylthiouracil, suggesting that the diastolic pressure remained unaffected. Thyroidectomy performed after the kidneys had been encapsulated for 9–19 weeks had only a slight effect on blood pressure.

Fregly & Cook *C*88,371/60: In rats, various thioureas inhibit the development of hypertension and cardiac hypertrophy following bilateral renal encapsulation. This effect is counteracted by feeding desiccated thyroid.

Mandel et al. *D*6,027/60: In rats, the compensatory renal hypertrophy and RNA synthesis in the remaining kidney, which normally occur after uninephrectomy, are inhibited by propylthiouracil.

Eades Jr. et al. *F*89,204/67: In rats with renal hypertension (uninephrectomy + figure-

of-8 ligature), propylthiouracil inhibits hypertension and coronary atherosclerosis but not the hypercholesterolemia.

Lefort et al. *G*46,725/67: In rats, metastatic calcification produced by bilateral nephrectomy is largely inhibited by calcitonin but uninfluenced by thyroxine pretreatment. Presumably the previously demonstrated protective effect of thyroxine against exogenous parathyroid hormone depends upon the presence of the kidney.

Côté et al. *G*46,741/68: In rats, calcitonin inhibits the metastatic calcification and bone lesions induced by bilateral nephrectomy. In nephrectomized animals, thyroxine does not modify the changes induced by endogenous hyperparathyroidism consequent to bilateral nephrectomy. "Presumably, to be effective against soft-tissue calcification and bone resorption induced by parathyroid extract overdosage, thyroxine requires the presence of the kidney."

Eades Jr. et al. *H*9,590/69: In rats with renal hypertension produced by uninephrectomy and a meat diet, thiouracil or sulfadiazine diminishes the blood pressure and protects the remaining kidney from damage.

Gardell et al. *G*70,430/70: In rats, the cardiovascular calcification produced by bilateral nephrectomy is not significantly influenced by ethylestrenol, CS-1, spironolactone, norbolethone, oxandrolone, prednisolone, progesterone, triamcinolone, DOC, estradiol or thyroxine.

Blood-Vessel Ligatures ←

Dau & Weber *G*20,433/63: Contrary to earlier claims, the recovery of the spinal cord (disappearance of motor disturbances) after temporary aorta ligature is not significantly influenced by "blockade of the thyroid" through pretreatment with iodine or KClO_4 in rabbits.

Ionizing Rays ←

In the mouse, according to most investigators, resistance to X-irradiation is decreased by thyroid hormones and increased by thioureas. However, some workers claim that neither thioureas nor thyroidectomy influences X-ray resistance significantly in this species. The timing and dosage of the thyroid treatment also appears to be important since in one series of observations, pretreatment with thyroid extract until five days before X-irradiation diminished the resulting mortality induced by X-irradiation.

In rats also, pretreatment with thyroid hormones generally diminishes X-ray resistance, whereas thiouracil offers little if any protection. Indeed, it has been stated that conjoint treatment with thyroxine and thiourea induces the greatest drop in X-ray resistance.

In rabbits, both systemic damage following total body irradiation, and the renal changes induced by topical X-irradiation of the kidney, are aggravated by thyroxine and T3.

The thyroxine-induced differentiation of limb-buds in toad tadpoles is only insignificantly retarded by X-irradiation.

In the goldfish, as in mammals, thyroxine diminishes X-ray resistance.

MOUSE

Blount & Smith B30,000/49: In mice exposed to total X-irradiation, mortality was greatly increased by feeding desiccated thyroid and insignificantly diminished by thiouracil.

Haley et al. B49,990/50: Contrary to earlier claims, no protection against X-irradiation could be obtained in mice given large doses of thiouracil, propylthiouracil or methylthiouracil.

Limperos & Mosher B49,737/50: In mice, pretreatment with thiourea increases resistance to X-irradiation.

Mole et al. D96,011/50: In mice, thiourea reduces mortality following whole body X-irradiation.

Haley et al. B58,913/51: In rats, thyroparathyroidectomy offers no protection against X-irradiation. The small degree of protection noted by previous investigators after thiouracil may have been due to its sulphydryl group. On the other hand, thyroxine causes a significant increase in mortality rate, though not in total mortality.

Smith B66,170/51: In mice, thyroid feeding increases the mitotic index of the epidermis, but does not influence the effect of X-irradiation upon epidermal mitotic proliferation.

Pospíšil & Novák C67,534/58: Mice pretreated with thyroid extract until 5 days before X-irradiation were more resistant than unpretreated mice against mortality induced by ionizing rays. These findings are in sharp contrast with those of earlier authors who have found an increased mortality in animals given thyroid both before and during, or even continuing after X-irradiation.

Léonard & Maisin E26,654/63: In mice, β -aminoethylisothiourea offers moderate protection against the toxic effects of X-irradiation.

Maisin et al. E36,751/63: In mice, the protection against X-irradiation offered by

2β -aminoethylisothiourea (AET) is only slightly improved by concurrent administration of 5-HT.

RAT

Haley et al. B60,616/51: In rats, pretreatment with thiourea or thyroxine did not significantly alter mortality after X-irradiation. However, an increase in mortality rate was observed in animals which had received both thyroxine and thiourea.

Smith & Smith B60,347/51; B60,348/51: In rats, desiccated thyroid or dinitrophenol increased radiation lethality, but thiouracil and propylthiouracil exerted no significant protective effect.

Haley et al. G71,834/52: In rats, mortality after X-irradiation is increased both by propylthiouracil and by thyroxine.

Stender & Hornykiewytsch C37,079/55; C37,086/55: In rats the lethal effect of total body X-irradiation is diminished by a reduction in the oxygen tension of the surrounding air. This protective effect is counteracted by cortisone, adrenalectomy, and thyroxine.

Darcis & Brisbois C50,953/57: In the rat, the sensitivity of the small intestine to topical X-irradiation (unlike that of the vagina) is not influenced by thyroxine or testosterone.

Krahe & Kunkel C77,236/58: In rats, pretreatment with thyroxine decreases resistance to X-irradiation.

Shellabarger et al. D39,218/62: In female rats, the production of mammary cancers by X-irradiation is inhibited by diethylstilbestrol in doses which in themselves are not carcinogenic. T3 did not influence carcinogenesis under these circumstances.

Caprino & Gallina G13,680/63: Contrary to earlier claims, propylthiouracil does not offer significant protection against total body X-irradiation in rats.

Greig et al. E60,304/65: In rats, irradiation of the thyroid inhibits its capacity to undergo hyperplasia under the influence of a goitrogen. Pretreatment with methylthiouracil before irradiation reduces the degree of this inhibition.

Akoev et al. F73,202/66: Both stilbestrol and thyroid extract offered some protection against ^{60}C γ -radiation in rats.

Srebo et al. H32,848/70: In rats, thyroxine decreases, whereas propylthiouracil increases, resistance to subsequent X-irradiation.

Slebdodzinski and Srebo H29,972/71: In rats, thyroxine pretreatment aggravates the syndrome of total body irradiation, whereas propylthiouracil offers considerable protection.

RABBIT

Vittorio et al. C76,156/59: Rabbits treated with a mixture of thyroxine and T3 became unusually sensitive to the lethal effect of X-irradiation. Neither untreated nor methimazole treated rabbits succumbed after the dose of irradiation used.

Caldwell et al. D54,096/63: In rabbits, renal damage produced by topical X-irradiation of the kidney is aggravated by T3.

FISH, TOAD

Allen & Ewell C92,110/59: In tadpoles of *Bufo boreas halophilus*, thyroxine-induced differentiation of limb-buds is only insignificantly retarded by X-irradiation.

Srivastava et al. G23,764/64: In the goldfish (*Carassius auratus L.*), resistance to X-irradiation is diminished by thyroxine the same as in mammals.

VARIA

Rigat C10,747/55: Review (46 pp., 67 refs.) on the literature concerning the effect of hormones upon X-irradiation, with special reference to ACTH, STH, vasopressin, epinephrine, cortisone, DOC, testosterone, estradiol, progesterone, and thyroxine.

Hypoxia ←

In the rat, thyroid hormones increase whereas thyroidectomy and thioureas decrease sensitivity to hypoxia. This phenomenon became the basis of what was known as "Asher's method" for testing thyroid function. Pretreatment with thyroxine also predisposes the liver and the brain of the rat to the production of degenerative changes by hypoxia.

Similar observations have subsequently been confirmed by numerous investigators in the mouse in which the sensitization by thyroxine is so consistent and evident that it was made the basis of the Emmens and Parkes "closed vessel technique" for the bioassay of thyroid preparations. If mice are placed in closed vessels, the speed of their mortality during the developing anoxia is proportional to the amount of thyroid hormone with which they have been pretreated. T3 is about five times as active as thyroxine in this respect. The sodium salt of L-thyroxine is about seven times more potent than that of D-thyroxine. Among a series of T2 compounds only 3:5-diiodo-L-thyronine was effective, but even this was much less active than T3.

In rabbits and dogs, thyroidectomy diminishes the protein catabolic effect of hypobaric oxygenation and of several other stressors.

In guinea pigs, thyroidectomy is said not to affect resistance to lack of oxygen, whereas T3 has been claimed actually to increase it.

Fish and various other species are made unusually resistant to asphyxia by thioureas.

RAT

Klinger 51,094/18: Contrary to earlier claims, thyroparathyroidectomized rats do not tolerate hypoxia better than normals; in fact, they become hypersensitive to it.

Streuli 32,220/18: In rats, thyroidectomy increases resistance to hypoxia. Splenectomy has an opposite effect, and rats simultaneously thyroidectomized and splenectomized exhibit a normal resistance to hypoxia.

Duran A 10,045/20: In rats, thyroid extract increases, whereas thyroideectomy decreases sensitivity to hypobaric oxygenation.

Cameron & Carmichael 42,188/26: In young rats, thyroid feeding produces a predisposition for tetany; in animals so treated, diminished oxygen tension rapidly induces tetanic convulsions.

Rydin 22,940/28: In rats, thyroxine pretreatment increases sensitivity to hypobaric oxygenation.

Asher & Wagner 23,903/29: Both rats and guinea pigs become highly sensitive to anoxia after pretreatment with thyroid extract. This phenomenon is the basis of what the authors describe as "Asher's method for the testing of thyroid function by lack of oxygen."

Houssay & Rietti 3,187/32: In rats, pretreatment with an impure pituitary extract diminishes resistance against hypoxia, but this effect is abolished by thyroideectomy and is presumably due to TTH. In untreated rats, thyroideectomy actually increases resistance to anoxia.

McIver & Winter B 33,399/43: In rats pretreated with thyroxine, exposure to diminished atmospheric oxygen tension causes hepatic injury.

Goldsmith et al. B 333/45: Thiouracil and thiourea increase the resistance of rats to lowered barometric pressure. Estradiol and stilbestrol are ineffective in themselves and fail to influence the action of the antithyroid compounds.

Gordon et al. B 761/45: Review of the literature, and personal observations on the raised resistance to lowered barometric pressures induced in rats by thiourea, para-aminobenzoic acid (PABA), and other agents interfering with the thyroid function.

Blood et al. B 48,970/49: As judged by observations in rats pretreated with thyroxine or thiouracil "oxygen availability becomes a limiting factor in oxygen consumption only at altitudes approaching 40,000 feet in normal rats, but at much lower altitudes in animals whose metabolism has been stimulated by cold or by thyroxin."

Bargeton et al. B 50,869/49: In rats, pretreatment with thiouracil increases resistance against reduced barometric pressure.

Zarrow et al. B 63,316/51: In rats exposed to hypobaric oxygenation, thyroxine diminished survival time, whereas in mice it caused an initial increase followed by a decrease. Thiouracil enhanced survival time in rats and, to a much lesser extent, in mice also.

Flückiger & Verzár B 86,489/52: In rats, thyroideectomy does not markedly influence the development of hypothermia upon exposure to decreased oxygen pressure.

DeBias D 41,419/62: The survival of rats exposed to reduced oxygen tension was not significantly altered by thyroideectomy.

Riedel F 22,473/64: In rats and rabbits, chronic thyroxine overdosage produces morphologic changes in the brain, which are aggravated by hypoxia.

Keminger G 42,501/66: In rats, death from lack of oxygen in closed vessels is accelerated by T₃, and retarded after thyroideectomy or cortisone treatment. Epinephrine further accelerates mortality in hyperthyroid animals.

Trojanová G 42,905/66: In newborn rats, the survival of the respiratory centre (gasping) during anoxia is greatly reduced by thyroparathyroidectomy.

Smoake & Mulvey Jr. H 23,262/70: In rats, thyroideectomy and propylthiouracil increase, whereas feeding of desiccated thyroid decreases resistance to hypobaric hypoxia.

MOUSE

Emmens & Parkes B 4,928/47: Male mice are considerably more sensitive than females to anoxia (closed vessel technique). Various thyroid preparations increase sensitivity to anoxia.

Smith B 4,939/47: In mice, thyroxine shortens, whereas thiourea prolongs, survival in closed vessels. L-thyroxine is considerably more active than d-thyroxine. T₂ is even less active, whereas thyroxamine, diiodothyronamine, tetrachlorothyronine, tetrabromothyronine, and T₂ are inactive.

Reisfield & Leathem B 46,491/50: In mice, survival in closed vessels is reduced by thyroid globulin p.o., but unaffected by propylthiouracil.

Basil et al. B 53,039/50: The mouse anoxia test has been found useful in assaying the biologic activity of various thyroxine derivatives.

Smith & Smith B 60,348/51: In mice, desiccated thyroid or thyroxine pretreatment decreases resistance to progressive hypoxia or forced muscular exercise. Death may have been due to cardiac failure. "Irradiated mice, whether given thyroid or not, lived longer in the closed vessel and were still alive at lower O₂ concentrations than their corresponding controls."

Gemmill B 85,291/53: In mice, T₃ is only slightly more potent than thyroxine as judged by the anoxia test.

Anderson B94,669/54: In mice, T₃ is about 5 times as active as thyroxine in increasing sensitivity to anoxia.

Tabachnick et al. C22,161/56: "Using the mouse anoxia assay, Na L-thyroxine was found to be seven times more potent than Na D-thyroxine."

Tomich et al. C83,307/60: Six iodo-L-thyronines, viz. 3:3':5'-triiodo-, 3:5-diiodo-, 3:3'-diiodo-, 3':5'-diiodo, 3-moniodo-, and 3'-moniodo-L-thyronine, have been compared with 3:5:3'-triiodo-L-thyronine, in mice by the anoxia method. The only compound with any significant activity was 3:5-diiodo-L-thyronine but even this was much less active than 3:5:3'-triiodo-L-thyronine.

Wiberg et al. E23,265/63: The mouse anoxia test performed after thiouracil treatment permits simultaneous assessment of survival and goitre prevention. The antigoitrogenic assay is more sensitive and permits greater precision than the anoxia test in the bioassay of thyroactive materials.

RABBIT

Mansfeld & Müller 35,416/11: In rabbits, thyroidectomy inhibits the protein catabolic

effect of exposure to decreased oxygen tension, hydrocyanic acid intoxication, or fasting.

GUINEA PIG

Stämpfli 931/27: In guinea pigs, thyroidectomy does not significantly alter resistance to lack of oxygen.

Lamarche & Pluche F68,410/66: In guinea pigs, resistance to hypobaric oxygenation is increased by T₃ but not by triiodothyroacetic acid.

FISH

Tinacci B28,546/47: Fish (*Mustelus laevis*) pretreated with various thioureas become unusually resistant to asphyxia.

VARIA

Mansfeld 11,881/20: In rabbits and dogs, thyroidectomy diminishes the protein catabolism normally observed after intoxication with hydrocyanic acid, hemorrhage, or hypobaric oxygenation.

Hári 40,209/21: Polemic remarks concerning the technique and interpretation of earlier data on the effect of thyroidectomy upon the resistance to cyanides, chloroform, bacterial toxins, and oxygen deficiency.

Hyperoxygenation ←

In rats exposed to six atmospheres of oxygen in a pressure chamber, resistance is diminished by thyroxine. Similar diminutions of tolerance for hyperoxygenation have been noted with various other thyroid preparations, whereas thioureas have an opposite effect.

In the cat also, thyroid extract increases, whereas thyroidectomy decreases sensitivity to oxygen poisoning.

Campbell A14,903/37: In rats exposed to six atmospheres of oxygen in a pressure chamber, subsequent decompression is better tolerated at low than at high external temperatures. "Using an external temperature of 24°C and white rats of about 80 g., the following substances, administered subcutaneously, are found to enhance oxygen poisoning: thyroxin (0.4 mg), dinitrophenol (1.5 mg), ac-tetrahydro-β-naphthylamine (0.5 c.c., 1 p.c.), adrenaline (0.02 mg), pituitary extract (posterior lobe, above 3.5 units), insulin (0.025 u.) and eserine (0.045 mg administered with atropine 0.075 mg). These doses in themselves are harmless."

Gersh & Wagner B1,140/45: In cats, thyroid extract increases, whereas thyroidectomy decreases sensitivity to the convulsive effect of oxygen poisoning.

Grossman & Penrod B36,303/49: In rats exposed to high oxygen tension, the mortality is increased by pretreatment with desiccated thyroid, and decreased by propylthiouracil.

Bean & Bauer B76,951/52: In rats, desiccated thyroid augments the adverse effects of exposure to high-oxygen tension. It also abolishes the protective effect of hypophysectomy.

Taylor C47,861/58: In rats "adrenalectomy gave very definite protection against

the central nervous system manifestations of oxygen poisoning, and gave some protection against lung damage." Adrenocortical extract and cortisol increased susceptibility of adrenalectomized animals to oxygen poisoning, whereas cortisone, DOC, and thyroid powder had no such effect.

Smith et al. C95,244/60: In rats, desiccated thyroid or thyroxine increases the noxious

effects of breathing virtually pure oxygen at atmospheric pressure. Conversely, hypophysectomy increases resistance to oxygen, presumably through the elimination of TTH.

Szilagyi et al. G68,248/69: In rats and rabbits, mortality from hyperbaric oxygenation is increased by pretreatment with thyroid extract, but uninfluenced by thyroidectomy.

Temperature Variations ←

In rabbits, thyroid hormones increase resistance to cold, and conversely, tolerance to desiccated thyroid is augmented in a cold environment. Thyroparathyroidectomy and thioureas diminish cold resistance. Tolerance to a warm environment is decreased by desiccated thyroid.

In rats, sensitivity to warm surroundings also rises after pretreatment with thyroid preparations, whereas resistance to cold is increased. Thyroidectomy and thioureas diminish cold resistance. In rats fed thyroid, exposure to cold causes marked pentosuria, whereas thiouracil has an opposite effect. The decreased ability of old rats to adapt themselves to cold is also improved by T3. In thyroidectomized rats, resistance to cold is restored towards normal by intraocular thyroid transplants. The vitamin-A requirements of rats are greatly increased during exposure to cold unless they are pretreated with thiouracil.

In mice, thyroid feeding increases sensitivity to heat stroke and predisposes to the production of hepatic lesions during exposure to high temperature.

In hamsters, thyroidectomy diminishes cold resistance much less than in rats. However, radiothyroidectomy renders them sensitive to cold. Hamsters presumably possess ectopic thyroids which are not eliminated by ordinary thyroidectomy.

Thyroidectomized goats are also very resistant to cold, but this has been ascribed to increased epinephrine secretion.

In various strains of fish, heat tolerance is increased by thiourea. Immature salmon can be completely radiothyroidectomized and yet continue to grow, but their heat tolerance is impaired.

RABBIT

Cori 17,210/22: In rabbits, thyroidectomy diminishes resistance to cold and increases its hypothermic effect.

Draize & Tatum 3,901/31: The resistance of rabbits to survival at a temperature of 33°C is recommended as a basis for the bioassay of desiccated thyroid preparations.

Draize & Tatum 3,657/32: In rabbits, the tolerance for desiccated thyroid is increased in a cold and decreased in a warm environment.

Sanfilippo & Ricca 31,704/35: In rabbits, pretreatment with thyroxine increases resistance to cold.

di Macco 34,121/35: In rabbits, the hyperthermia induced by exposure to heat is aggravated by thyroxine.

Capitolo A1,730/36: In rabbits, thyroparathyroidectomy decreases the resistance to heat stroke, and death occurs at a lower body temperature level than in controls.

Martinengo & Beghelli B3,426/39: In rabbits, pretreatment with T2 diminishes resistance to heat.

Lange et al. B23,962/48: In rabbits, resistance to cold is increased by pretreatment with thyroid extract and diminished following partial suppression of thyroid function by thiouracil.

Medvedeva F96,027/68: Biochemical studies on the decreased cold resistance of thiourea-treated rabbits.

RAT

Abderhalden & Wertheimer 19,292/28: Rats pretreated with thyroxine are unusually sensitive to warm surrounding temperature.

Genitis et al. 68,723/35: In young thyro-parathyroidectomized rats, exposure to heat 24 hrs after the operation greatly increased the mortality rate, whereas cold surrounding temperature diminished it. The number of tetanic convulsions was greatest at an intermediate temperature. [From the brief abstract, it is difficult to differentiate between the role of parathyroid and of thyroid deficiency (H.S.).]

Barbour & Seavers 84,296/43: In rats, exposure to cold and an excess of CO₂ produce a state of narcosis against which considerable resistance can be induced by thyroid extract. No such effect was obtained by dinitrophenol.

Zarrow & Money B27,880/49: In rats, pretreatment with thiouracil diminishes the resistance to cold, a phenomenon which is ascribed to the adrenal cortical involution elicited by thiourea.

Blood et al. B48,970/49: As judged by observations in rats pretreated with thyroxine or thiouracil "oxygen availability becomes a limiting factor in oxygen consumption only at altitudes approaching 40,000 feet in normal rats, but at much lower altitudes in animals whose metabolism has been stimulated by cold or by thyroxine."

Roe & Coover B54,246/51: In rats, thyroid feeding or exposure to cold markedly increases urinary pentose excretion, whereas thiouracil reduces the output of urinary pentose and decreases resistance to cold. Apparently "the thyroid gland has a dominating role in the production of urinary pentose and that adjustment of animals to cold takes place, at least in part, through activity of the thyroid gland."

Sellers et al. B65,310/51: The survival of clipped rats exposed to cold is considerably prolonged by combined treatment with thyroxine + cortisone. Each of these agents alone has much less protective value, and DOC is inactive.

Money C5,393/54: Female rats lose their ability to resist a cold environment if they are pretreated with thiouracil.

Weiss C34,561/57: Studies on tissue metabolism in rats exposed to cold after thyroidectomy by ¹³¹I. "The hypothesis is advanced

the thyroid gland exerts its effects by way of a few selected tissues only, in which it regulates the level of metabolism so as to provide adequate heat production for suitable adaptation to cold of the entire animal."

Weiss C66,153/59: The decreased ability of old rats to adapt themselves to cold is greatly improved by T3.

Garrido D8,112/60: In rats, resistance to cold is increased by thyroxine and T3, and decreased by thyroidectomy or destruction of the thyroid with radio-iodine. Prednisolone exerted only a moderate protective effect.

Fregly D5,800/61: In rats, propylthiouracil does not reduce spontaneous running activity in itself, but when exposed to cold, rats thus treated do not increase their activity as much as controls.

Hsieh D20,969/62: Rats fed propylthiouracil for four weeks before exposure to cold died in about 17 days, while those fed an iodine-deficient diet and propylthiouracil, for the same period before exposure, died in less than one day. Rats maintained for four weeks in the cold and on T3 died when the dose levels of the thyroid hormone were reduced. "Thus cold adaptation does not reduce the requirement for thyroid hormone."

Beaton D55,998/63: Review of the literature, and personal observations on the effect of thyroid feeding or thyroidectomy upon the cold resistance of rats given diets of varying protein content.

Pavlovic-Hournac & Andrus E33,972/63: In rats, the decreased resistance to cold induced by thyroidectomy is restored towards normal by intraocular thyroid transplants.

Weiss G21,456/63: In rats, resistance to cold can be increased with T3 acetate as it can with T3 or thyroxine.

Hamburg & Lynn G21,782/64: In rats raised at 20°C, the delay in skeletal maturation induced by propylthiouracil is more severe than in controls raised at 30°C.

Hsieh F71,817/66: Systematic studies on the thyroid hormone (thyroxine, T3) requirements of thyroidectomized curarised rats for resistance to cold in the absence of shivering.

Weihe F69,421/66: In rats, thyroxine impedes acclimatization to high altitude.

Bauman & Turner F81,331/67: Pretreatment of rats with thyroxine raises their resistance to cold. Additional administration of corticosterone greatly increases this effect, although in itself, corticosterone possesses only a slight protective action.

Sundaresan et al. G50,127/67: The vitamin-A requirements of rats are greatly increased during exposure to cold, this increase is abolished by thiouracil.

MOUSE

Lübbe C12,952/56: In mice, thyroid feeding increases sensitivity to heat stroke and causes particularly severe hepatic lesions upon exposure to high temperature.

GUINEA PIG

Pfeiffer 16,694/23: In guinea pigs, thyroidectomy aggravates the drop in body temperature produced by cooling or salicylate injection i.p.

Amante & Mancini C21,222/56: In guinea pigs, pretreatment with methylthiouracil prolongs survival following severe burns. The data are discussed primarily in connection with the role of the thyroid in the alarm reaction.

HAMSTER

Chaffee et al. G71,307/63: In hamsters, thyroidectomy does not diminish cold resistance nearly as much as in the rat.

Yousef et al. F86,757/67: Hamsters, unlike rats, are very resistant to cold even after complete surgical thyroidectomy. In order to determine whether this difference is due to the existence of ectopic thyroids, radio-iodine was administered; since this caused an even more severe drop in plasma PBI than thyroidectomy, it was concluded that hamsters may possess accessory thyroid tissue. However, upon exposure to cold, the BMR rose significantly in both groups and yet, the surgically thyroidectomized hamsters survived, whereas most of the radio-thyroidectomized animals succumbed. Apparently, "increased thyroid activity in cold exposure has no significant effect upon survival" in this species.

Yousef et al. F98,470/68: Hamsters are resistant to cold even after surgical thyroidectomy, but not after treatment with ^{131}I . The plasma PBI is lowered by thyroidectomy, but not as much as by ^{131}I . Presumably the hamsters have ectopic thyroid tissue which permits survival after surgical thyroidectomy.

GOAT

Andersson et al. G45,246/67: Thyroidectomized goats maintain body temperature during exposure to acute cold (-3°C) and also react to cooling of the hypothalamic thermo-regulatory "centre" by a rise in body temperature. However, under these conditions, shivering and urinary catecholamine excretion were greatly increased. "It is concluded that to maintain thermal homeostasis in the cold markedly hypothyroid goats have to compensate the lack of thyroid hormone by a conspicuous increase in adrenaline secretion."

CAT

Boatman C68,449/59: In cats "thyroidectomy prior to cold exposure makes heat conservation responses less efficient than in the normal animal and the intact thyroid plays a role in maintaining body fluids in an efficient equilibrium for rapid adjustment to a cold environment."

FISH

Eyropeitzeva A 49,151/49: Larvae of the fish *Coregonus lavaretus ludoga* withstand exposure to 29°C for five min after treatment with thiourea, whereas untreated animals die.

La Roche & Leblond C434/54: Immature salmon can be completely "thyroidectomized" by radio-iodine; yet, they continue to grow, although their resistance to a rise in water temperature is greatly impaired.

Suhrmann D76,901/55: Immersion into a solution of thiourea increases the upper lethal temperature tolerated by goldfish (*Carassius auratus*).

Fortune C17,485/55; C21,670/56: In the minnow (*Phoxinus phoxinus L.*), the thermal death point is raised considerably by treatment with thiourea.

Cheverie & Lynn D68,411/63: In the fish (*Tanichthys albonubes*), inactivation of the thyroid by immersion into a thiourea solution slightly reduces tolerance to high temperatures. The literature on opposite results in other species of fish is reviewed.

Dodd & Dent E21,585/63: In minnows (*Phoxinus phoxinus L.*), neither thiourea nor thyroxine pretreatment induced any significant change of heat tolerance.

Electric Stimuli ←

In guinea pigs, the EST is diminished within two days after initiation of thyroid feeding, and augmented after thyroidectomy.

In rats, the EST is only insignificantly lowered by thyroidectomy. It is allegedly also diminished one hour after thyroxine administration but increased 18 hrs later. This biphasic response may explain some of the contradictions in the literature.

In mice, thyroxine facilitates the production of convulsions by electroshock, and in dogs, it increases irritability of the sympathetic nervous system.

Specht 13,475/23: In guinea pigs, neither thyroidectomy nor orchidectomy influences the course of the convulsions produced by amylnitrate inhalation or electric irritation of peripheral nerves.

Gerlich B49,124/49: In guinea pigs, the EST is diminished within two days after initiation of thyroid feeding. Thyroidectomy has an opposite effect.

Woodbury et al. B68,423/52: In rats, brain excitability (pentylenetetrazol, EST) decreases following thyroidectomy or treatment with propylthiouracil and increases after thyroxine pretreatment. There are however certain differences between thyroidectomy and propylthiouracil as regards the recovery time from electroshock seizures and their relative effect upon extensor and flexor components.

Thiébaut et al. C18,452/56: In dogs, thyroxine pretreatment increases the electric irritability of the sympathetic nervous system.

de Salva et al. C51,842/58: In rats, the EST was lowered by hypophysectomy and

adrenalectomy, but only insignificantly by thyroidectomy. 5-HT elevated the EST.

Pfeifer et al. D12,952/60: In rats, the convulsive effect of "Pentametazol" [presumably pentylenetetrazol (H.S.)] is diminished one hour after administration of thyroxine, but increased 18 hrs later. A corresponding biphasic response is also noted with regard to the EST. In mice, the increased motility induced by amphetamine is also inhibited during the first hour after thyroxine treatment. The possible biochemical reasons for this "negative tendency" during the early phase of thyroxine action are described.

de Salva D66,176/63: In rats, the EST is reduced in descending order of magnitude by adrenalectomy, hypophysectomy, and thyroidectomy. The effect of these endocrine deficiencies upon various depressant drugs is also described.

Pfeifer et al. G65,057/68: In mice, thyroxine facilitates the production of convulsions by pentylenetetrazol and electroshock. These effects are inhibited by various amphetamine derivatives.

Various Stressors ←

Dogs fed desiccated thyroid are particularly susceptible to traumatic shock, whereas methylthiouracil offers some protection against it. Similar observations have been made in rats. The formation of peritoneal adhesions in response to local injury is diminished by methylthiouracil.

In mice, thyroid preparations diminish resistance to forced muscular exercise.

In rabbits and dogs, thyroidectomy diminishes the protein catabolism that follows hemorrhage.

Following pretreatment with T3, the audiogenic seizures produced in susceptible mice by strong sound are accelerated in onset, but their pattern remains unchanged. T3 does not induce audiogenic seizure-proneness in nonsusceptible strains.

Trauma ←

Schachter & Huntington A32,970/40: Dogs fed desiccated thyroid are particularly susceptible to the production of traumatic shock by manipulation of their intestines.

D'Aste & Ardau B56,421/49: In dogs, methylthiouracil offers some protection against various forms of traumatic shock, but this effect is ascribed to the antihistaminic property of the drug.

Takács et al. C29,459/54: In rats, traumatic shock (produced by freezing the hind limbs) is diminished by methylthiouracil, but aggravated by thyroxine, thyroid extract, or dinitrophenol.

Dobrohotova C55,431/57: In rats, survival following hemorrhagic shock with trauma is prolonged by methylthiouracil.

Kováč et al. C50,699/57: In rats, survival from shock (produced by freezing a hind leg with liquid air) is shortened by thyroid feeding, thyroxine, dinitrophenol or epinephrine, all of which accelerate the metabolic rate. Conversely, methylthiouracil increases survival time.

Oppenheimer et al. C50,563/58: In goats, traumatic shock reduces the capacity of the thyroid to concentrate iodine, but recently thyroidectomized animals showed no change in survival times, although pretreatment with thyroxine greatly sensitized to traumatic shock. Cortisone had no effect upon survival following trauma nor did it counteract the aggravating effect of thyroxine.

Schachter et al. C63,544/59: In rats, pretreatment with cortisone, thyroxine, or both these agents shortened survival after tourniquet shock.

Németh & Vigaš F98,055/68: In rats, resistance to trauma in the Noble-Collip drum is reduced by pretreatment with thyroxine or dinitrophenol but increased by thyroidectionomy.

Rusakov & Chernov H9,072/69: In rabbits, the formation of adhesions by removal of the serosa of peritoneal organs is considerably

diminished by pretreatment with methylthiouracil.

Muscular Work ←

Smith & Smith B60,348/51: In mice, desiccated thyroid or thyroxine pretreatment decreases resistance to progressive hypoxia or forced muscular exercise. Death may have been due to cardiac failure. "Irradiated mice, whether given thyroid or not, lived longer in the closed vessel and were still alive at lower O₂ concentrations than their corresponding controls."

Valtin & Tenney C66,148/59: In rats, resistance to forced muscular exercise is diminished following pretreatment with T3.

Hemorrhage ←

Mansfeld 11,881/20: In rabbits and dogs, thyroidectionomy diminishes the protein catabolism normally observed after intoxication with hydrocyanic acid, hemorrhage, or hypobaric oxygenation.

Sound ←

Hamburg & Vicari C71,704/58; D11,010/60: In mice susceptible to audiogenic seizures, T3 does not change the seizure pattern nor does it induce seizures in nonsusceptible strains. It merely accelerates the onset of the period during which susceptible animals respond by convulsions to audiogenic stimulation.

Tumors ←

In rats, the production of cystic and neoplastic hepatic lesions by 2-acetaminofluorene is inhibited by thiouracil. The hepatic enlargement induced by Walker tumor transplants is also diminished by this goitrogen and restored by a subsequent thyroxine treatment.

The growth of transplanted fibrosarcomas is increased by thyroid extract or T3, and decreased by propylthiouracil. The lifespan of rats bearing transplantable leukemia is prolonged by thyroidectionomy, but in mice this does not seem to be the case.

Cantarow et al. B18,774/46: In rats given 2-acetaminofluorene p.o., the development of cystic and neoplastic hepatic lesions was accelerated and intensified by GTH (pregnant mare serum), estradiol, and testosterone, but inhibited by thiouracil. "This phenomenon may be related to the role of the liver in the intermediary metabolism and excretion of the sex

steroid." In the hyperplastic target organs of the sex hormones, tumors did not occur, in contrast to the high incidence of tumors in the thyroids of rats given thiouracil simultaneously with the carcinogens.

Murphy et al. C60,008/58: In mice, resistance to infection with *Candida albicans* or *Streptococcus pyogenes* is increased by pre-

treatment with T3, but this hormone does not significantly alter resistance to transplanted leukemia.

Girkin & Kampschmidt C 99,934/61: In rats, the hepatic enlargement induced by Walker tumor transplants or by partial hepatectomy is inhibited by thiouracil, and largely restored by subsequent thyroxine treatment.

Claus et al. D 29,754/62: In rats, the growth of transplanted fibrosarcomas was increased by thyroid extracts or T3 and decreased by propylthiouracil or an iodine-deficient diet.

Morris & Mokal D 65,803/63: In rats bearing transplantable leukemia, survival is prolonged by thyroidectomy.

Fisher & Fisher F 74,176/66: In rats, the incidence of metastases from Walker tumor

transplants is not significantly altered by thyroidectomy, propylthiouracil, thyroxine or TTH.

Varia ←

Smith C 46,496/56: In brown trout, thyroxine raises, whereas thiourea and thiouracil reduce salinity tolerance. Anterior pituitary extracts and STH likewise raise salinity tolerance, whereas posterior lobe extracts, testosterone, gonadotrophin, TTH, and ACTH have no such effect.

Czarnecki & Kiersz D 15,579/61: In dogs, shock produced by trypan blue or peptone injection is more powerfully inhibited by thyro-parathyroidectomy than by thyroidectomy.

Hepatic Enzymes ←

TPO activity is allegedly increased by thyroidectomy in the rat, and substrate-induced TPO synthesis is inhibited by thyroxine.

Hepatic GPT activity is moderately increased by thyroxine. α -GPDH activity is raised by T3 or thyroxine, but diminished by thyroidectomy or radiothyroidectomy.

TPO, TKT ←

Geschwind & Li B 93,277/54: In the rat, the induction of the TPO enzyme system is diminished by hypophysectomy and adrenalectomy, but increased by thyroidectomy.

Kulcsar et al. G 72,002/69: In rats, the substrate-induced synthesis of TPO was inhibited by hepatic injury (CCl_4) as well as by thyroxine. Thyroidectomy was without effect, and actually inhibited the influence of CCl_4 .

GPT ←

Rosen et al. C 71,414/59: Marked increases in GPT activity were observed in the livers of rats given cortisol, cortisone, 9 α -fluorocortisol, prednisone, 6 α -methylprednisolone, 9 α -fluoro-21-desoxy-6 α -methylprednisolone or ACTH, whereas two nonglucocorticoid cortisol derivatives, 11-epicortisol and 9 α -methoxy-cortisol were inactive. STH, testosterone, and insulin caused no significant change in GPT by themselves nor did they modify the action of cortisol. On the other hand, large doses of estradiol and thyroxine caused a moderate increase in GPT activity, but when injected simultaneously with cortisol, they appeared to

interfere with its action as did progesterone. Adrenalectomy slightly diminished or failed to affect the GPT inducing activity of cortisol, whereas hypophysectomy caused a rise in GPT activity and augmented the effect of cortisol.

SDH ←

Ishikawa et al. F 41,763/65: In alloxan-diabetic rats, SDH and TDH levels of the hepatic microsomes are greatly enhanced. SDH was readily induced by cortisol in the diabetic, but not in the normal, rat. The effects of actinomycin S, STH, and starvation upon serine dehydratase have also been studied in intact, hypophysectomized, adrenalectomized, and thyroidectomized rats. It is concluded that "serine dehydratase activity in the liver plays an important role in the production of pyruvate as a starting material for gluconeogenesis."

α -GDPH ←

Rivlin & Wolf H 13,055/69: In rats, the hepatic α -GPDH activity is greatly increased by T3 or thyroxine, but diminished by thyroidectomy or ^{131}I treatment. Both the basal

α-GPDH activity and the maximal increment induced by triiodothyronine are dependent upon adequate intake of riboflavin.

Other Enzymes ←

Spinks & Burn B72,891/52: Thyroid feeding diminishes the amine oxydase activity of the liver in rabbits, whereas thyroideectomy increases it both in rabbits and in rats.

Metzenberg et al. D86,024/61: Thyroxine induces carbamyl phosphate synthetase in hepatic microsomes of the liver in tadpoles.

Freedland F46,702/65: In hepatic homogenates of rats pretreated with thyroxine "there was a marked increase in glucose-6-phosphatase, a decrease in phosphorylase, and relatively smaller changes in other glycolytic enzyme activities after treatment. The enzymes of the

pentose phosphate pathway increased as did malic enzyme activity, although a fourth TPN-linked dehydrogenase, isocitric, decreased. L-*α*-Glycerolphosphate dehydrogenase decreased in the hyperthyroid animals. All 3 of the tricarboxylic acid cycle enzymes measured increased in activity after thyroxine injection."

Kato & Takahashi H11,853/69: "The magnitude of increase in the activities of microsomal drug-metabolizing enzymes and NADPH-linked electron transport system in the alloxan diabetic rats was greater than in normal rats, in contrast, the magnitude of increase in the thyroxine-treated rats was smaller than in normal rats."

Kato et al. H11,851/69: Studies on the effects of thyroxine upon hepatic microsomal enzyme induction by various drugs in diverse species.

← PARATHYROIDS

Comparatively few investigators have examined the effect of the parathyroids on resistance in general.

Steroids ← cf. *Selye C50,810/58, p. 89; C92,918/61, pp. 77, 164, 280; G60,083/70, pp. 410, 412.*

Hormones and Hormone-Like Substances ←

The effect of the parathyroids on the action of steroids has been discussed elsewhere. (For references cf. Abstract Section.) Parathyroidectomized dogs are allegedly much less resistant against histamine than intact controls, and in rabbits, parathyroid extract protects against histamine, insulin, and a number of other toxicants. However, these early experiments require confirmation.

Histamine ←

Dragstedt et al. I7,561/23: "Parathyroidectomized dogs are much less resistant to guanidine, methyl-guanidine, trimethylamine, histamine, and the various intestinal poisons than are normal dogs."

McDonagh 19,285/28: In rabbits, parathyroid extract protects against the toxic effects of histamine, insulin, guanidine, coniine and

"somnifaine" [superficial description of observations which do not inspire confidence (H.S.)].

Insulin ←

McDonagh 19,285/28: In rabbits, parathyroid extract protects against the toxic effects of insulin [superficial description of observations which do not inspire confidence (H.S.)].

Epinephrine ← cf. *Selye C92,918/61, p. 194; G60,083/70, pp. 410, 413.*

Drugs ←

The parathyroids play an important role in resistance only against very few drugs. Even the effects of such compounds as copper or beryllium salts which cause definite bone changes are not markedly influenced by parathyroid extract.

It has been claimed that in mice, parathyroid extract can protect against fatal fluoride intoxication, but this has been denied by subsequent investigators.

During the early part of this century, it was assumed that parathyroidectomy causes tetany because it interferes with the detoxication of guanidine, but this could not be confirmed.

On the other hand, the topical calcification produced by indium chloride in the rat is prevented by parathyroidectomy, although the associated hepatic necrosis and icterus remain unaffected. Pretreatment with parathyroid extract (or DHT) prevents the hepatic necrosis, but augments the topical calcergy.

Resistance to $MgSO_4$ i.v. is increased by parathyroid extract in the dog, presumably because of the well-known antagonism between Ca-and Mg-ions. In mice, parathyroid extract inhibits the development of Mg-anesthesia in a dose-dependent manner.

The nephrocalcinosis induced by a dietary excess of phosphate (NaH_2PO_4) in the rat is inhibited by thyroparathyroidectomy as well as by excessive thyroxine administration.

The production of cardiovascular lesions by "standard renal injury" following treatment with sulfa drugs is prevented by thyroparathyroidectomy in the rat — as is the osteitis fibrosa produced by uranium intoxication — probably because these toxicants elicit renal damage with secondary hyperparathyroidism. The latter is presumed to be responsible for the disturbances in skeletal metabolism.

The calcinosis elicited by vitamin-D compounds, including DHT, is not prevented by parathyroidectomy; hence it cannot be ascribed to a secondary hypersecretion of parathyroid hormone as had been originally thought.

Anaphylactoidogens ← cf. Selye G 46,715/
68, pp. 179, 199.

Antibiotics ← cf. Selye C 92,918/61, p. 91;
G 60,083/70, pp. 410, 413.

Barbiturates ←

McDonagh 19,285/28: In rabbits, parathyroid extract protects against the toxic effects of histamine, insulin, guanidine, coniine and "somnifaine" [superficial description of observations which do not inspire confidence (H.S.)].

Copper ←

Ulmansky & Sela G 70,273/69: In mice, copper administration causes thickening, and fluoride treatment thinning, of the epiphyseal plates. Neither of these responses is influenced by parathyroid extract, which in itself causes some thickening of epiphyseal plates.

Beryllium ←

Jones 33,139/35: In dogs with beryllium rickets, parathyroid extract failed to raise the blood calcium.

Coniine ←

McDonagh 19,285/28: In rabbits, parathyroid extract protects against the toxic effects of histamine, insulin, guanidine, coniine and "somnifaine" [superficial description of observations which do not inspire confidence (H.S.)].

Digitoxin ←

Selye PROT. 33541, 34074: In rats, PCN is highly efficacious in preventing digitoxin poisoning, even after parathyroidectomy, thyroparathyroidectomy, or concurrent treatment with propylthiouracil (PTU). No protection was obtained by thyroidectomy, parathyroidectomy, or treatment with PTU, thyroxine, parathyroid extract or calcitonin. Apparently, the goitrogenic effect of PCN plays no indispensable role in its catatoxic action.

Fluoride ←

Kochmann 55,947/34: In mice, fatal intoxication with NaF or oxalic acid can be prevented by pretreatment with parathyroid

extract. These inhibitions are dose-dependent and may serve for the assay of parathyroid preparations.

Muñoz 67,126/36: In rats, parathyroid extract fails to prevent the manifestations of fluorosis.

Ulmansky & Sela G70,273/69: In mice, copper administration causes thickening, and fluoride treatment thinning, of the epiphyseal plates. Neither of these responses is influenced by parathyroid extract, which in itself causes some thickening of epiphyseal plates.

Guanidine ←

Dragstedt et al. 17,561/23: "Parathyroidectomized dogs are much less resistant to guanidine, methyl-guanidine, trimethylamine, histamine, and the various intestinal poisons than are normal dogs."

Süssmann 24,462/27: In mice, very impure parathyroid extracts protect against guanidine and picrotoxin but not against strychnine.

McDonagh 19,285/28: In rabbits, parathyroid extract protects against the toxic effects of histamine, insulin, guanidine, coniine and "sommifaine" [superficial description of observations which do not inspire confidence (H.S.)].

Indium ←

Selye et al. D25,667/62: In rats, InCl_3 s.c. produces topical calcification and severe hepatic necrosis with icterus. Parathyroidectomy prevents the topical (calceric) calcification at the injection site, but not the hepatic necrosis. Pretreatment with parathyroid extract (or with DHT) prevents the hepatic necrosis, although it augments the local tissue calcification at the injection site.

Magnesium ←

Matthews & Austin 21,067/27: In dogs, resistance to MgSO_4 i.v. is increased by parathyroid extract, and decreased by parathyroidectomy, presumably because of the well-known antagonism between Ca-and Mg-ions.

Simon 31,369/35: In mice, parathyroid extract inhibits the development of magnesium narcosis in a dose-dependent manner. This phenomenon can be used for the standardization of parathyroid preparations.

Perchlorate ← cf. *Selye C92,918/61, p. 280.*

Permanganate ← cf. *Selye D15,540/62, p. 303.*

Oxalate ←

Kochmann 55,947/34: In mice, fatal intoxication with NaF or oxalic acid can be prevented by pretreatment with parathyroid extract. These inhibitions are dose-dependent and may serve for the assay of parathyroid preparations.

Peptone ←

Czarnecki & Kiersz D15,579/61: In dogs, shock produced by trypan blue or peptone injection is more powerfully inhibited by thyroparathyroidectomy than by thyroidectomy.

Phosphate ← cf. also *Selye G60,083/70, p. 410.*

Selye C38,627/58: In rats, the nephrocalcinosis produced by a dietary excess of NaH_2PO_4 is inhibited both by thyroparathyroidectomy and by excess thyroxine administration.

Picrotoxin ←

Süssmann 24,462/27: In mice, very impure parathyroid extracts protect against guanidine and picrotoxin, but not against strychnine.

Potassium ←

Thatcher & Radike B4,515/47: In rats, resistance to KCl intoxication was increased by DOC or adrenocortical extract. Parathyroid extract decreased potassium resistance.

Puromycin Aminonucleoside ←

Johnston & Follis Jr. D12,799/61: In rats, the osteitis fibrosa-like changes produced by puromycin aminonucleoside (PAN) are not prevented by parathyroidectomy.

Salicylates ←

Abbott & Harrisson F36,510/65: In rats, cancellous bone formation is stimulated by various salicylates. This effect is blocked by parathyroid extract and vitamin D, but not influenced by cortisone.

Strychnine ←

Süssmann 24,462/27: In mice, very impure parathyroid extracts protect against guanidine and picrotoxin, but not against strychnine.

Sulfa Drugs ← cf. also *Selye C92,918/61, p. 194; G60,083/70, pp. 413, 414.*

Lehr & Martin C13,119/56: In rats, the production of cardiovascular lesions by "standard renal injury" (due to treatment with sulfa drugs) is prevented by thyroparathyroidectomy, but not by thyroidectomy with parathyroid extract treatment. Curiously, "chemical thyroidectomy" [technique not specified (H.S.)] also inhibited, and thyroid hormone excess aggravated these lesions.

Lehr & Martin C23,011/56: In rats, the cardiovascular lesions produced by sodium acetyl sulfathiazole (as a consequence of renal injury) are prevented by thyroparathyroidectomy, presumably because in the final analysis, the changes observed are due to nephrogenic hyperparathyroidism.

Lehr C84,326/59: In rats, the role of parathyroid hormone in the production of cardiovascular lesions by renal damage (Na-acetylsulfathiazole, surgery) was subjected to systematic analysis.

Okano et al. H25,894/70: In rats, the calcification and necrosis of the aortic media induced by the "obstructive nephropathy" developing after injection of sodium sulfacetylthiazole (SAT) can be prevented by thyroidectomy, and to a lesser extent by calcitonin.

Uranium ←

Eger B35,694/42: In rats, the osteodystrophy fibrosa produced by uranium intoxication can be prevented by parathyroidectomy, presumably because the renal damage induced by the heavy metal acts on the bones only through the intermediary of the parathyroids.

Vitamin A ← cf. Selye G60,083/70, pp. 410, 413.

Vitamin C ←

Kalnins & Ledina B19,372/47: In guinea pigs, parathyroid extract accelerates the development of scorbutic changes on a vitamin-C deficient diet.

Vitamin D, DHT ← cf. Selye C92,918/61, p. 176; D15,540/62, p. 281; G60,083/70, pp. 408, 410.

Diet ← cf. also Selye G60,083/70, pp. 410, 413.

Dragstedt & Peacock 17,556/23: In dogs, parathyroid tetany is highly subject to modification by certain diets. It is concluded that "the parathyroid glands do not furnish a hormone necessary for life, and dogs may be kept alive indefinitely after their removal if treatment directed to the prevention of this toxemia of intestinal origin is carried out."

Bacteria ←

In guinea pigs, parathyroid extract allegedly delays the course of experimental tuberculosis, whereas in rats removal of the parathyroids has been claimed to lower resistance to this infection. In mice, parathyroid extract offers some protection against infection with *P. anthracis*, *E. coli* or *Ps. pyocyaneus* but not against *Klebsiella pneumoniae*.

Bacterial Toxins ←

In dogs and rabbits, tetanus intoxication is not significantly affected by parathyroid extract, but the spread of this toxin is allegedly delayed by parathyroid preparations in the mouse.

Renal Lesions ←

Hypertension produced by unilateral renal artery constriction in rats is not significantly affected by parathyroidectomy. However, the cardiovascular calcification produced by nephrectomy and by certain renal lesions in the rat can be prevented by thyroidectomy presumably because here the calcinosis is a secondary result of increased parathyroid hormone secretion.

In rats, calciphylaxis produced by bilateral nephrectomy + ferric dextrin is prevented by thyroidectomy. From this it was concluded that endogenous parathyroid hormone in amounts secreted by the gland can act as a calciphylactic sensitizer.

Stressors ←

Several investigators claimed that the parathyroids play an important part in resistance to cold, X-irradiation and other forms of stress, but all these findings require confirmation.

Bacteria ←

Pelouze & Rosenberger 62,508/24: In guinea pigs, parathyroid extract or calcium feeding delays the course of experimental tuberculosis.

Steinbach 92,528/32: In rats, parathyroidectomy lowers resistance to infection with bovine but not with human tuberculosis. Thyroparathyroidectomy makes rats susceptible to both human and bovine tubercle bacilli.

Weinstein B 15,029/39: In mice, various anterior pituitary preparations protect against infection with *B. anthracis*. Parathyroid extract was also very effective, whereas thyroxine and testosterone offered little protection, and progesterone, insulin, "estrin" and posterior lobe extract were virtually ineffective.

Weinstein A 33,940/40: In mice, neither parathyroid extract nor a crude anterior pituitary preparation offered protection against infection with *Klebsiella pneumoniae*, but they did improve survival after inoculation of *E. coli* or *Ps. pyocyaneus*.

Schäfer B 99,955/54; G 58,597/54: Monograph (127 pp., numerous refs.) on the role of endocrine factors in tuberculosis. Special sections are devoted to the hormones of the thyroid, parathyroid, thymus, adrenals, pancreas, and gonads.

Bacterial Toxins ←

Lissák 29,256/34: In dogs and rabbits, tetanus intoxication is not significantly modified by parathyroid extract.

Weinstein A 33,940/40: In mice, parathyroid extract prevents the spread of tetanus toxin from the site of inoculation and delays death.

Quattrocchi & Foresti G 43,535/66: Anaphylactic shock in guinea pigs and the Shwartzman-Sanarelli phenomenon in rabbits are inhibited by pretreatment with parathyroid extract. [The statistical significance of the apparent differences has not been appraised (H.S.).]

Immune Reactions ←

Quattrocchi & Foresti G 43,535/66: Anaphylactic shock in guinea pigs and the Shwartzman-Sanarelli phenomenon in rabbits are inhibited by pretreatment with parathyroid extract. [The statistical significance of the apparent differences has not been appraised (H.S.).]

Renal Lesions ←

Quadri 45,920/06: In rabbits, i.v. injection of a parathyroid extract ("Paratiroidina") prolongs survival following bilateral ureter ligation. This fact is ascribed to an antitoxic action of the parathyroid hormone, although the hormonal activity of the extract has not been ascertained.

Bein et al. C 57,714/58: In male rats with hypertension produced by unilateral renal artery constriction, vascular lesions are more common than in females. Gonadectomy does not significantly alter these changes in males, but aggravates them in females. Parathyroidectomy has no significant effect upon them.

Lehr C 84,326/59: In rats, the role of parathyroid hormone in the production of cardiovascular lesions by renal damage (Na-acetyl-sulfathiazole, surgery) was subjected to systematic analysis.

Selye et al. D 32,610/63: In rats, calciphylaxis produced by bilateral nephrectomy + ferric dextrin can be prevented by parathyroidectomy. Hence, it may be concluded that autogenous parathyroid hormones in amounts secreted by the glands can act as calciphylactic sensitizers.

Stressors ←

Genitis et al. 68,723/35: In young thyroparathyroidectomized rats, exposure to heat 24 hrs following the operation greatly increased the mortality rate, whereas cold surrounding temperature diminished it. The number of tetanic convulsions was greatest at an intermediate temperature. [From the brief abstract it is difficult to differentiate between the role of parathyroid and of thyroid deficiency (H.S.).]

Sanfilippo 56,085/35: In rabbits, parathyroid extract increases resistance to cold.

Rixon et al. C61,789/58: In rats, parathyroid extract prolongs survival after X-irradiation.

Czarnecki & Kiersz D15,579/61: In dogs, shock produced by trypan blue or peptone injection is more powerfully inhibited by thyro-parathyroidectomy than by thyroidectomy.

← CALCITONIN

Parathyroid Hormone ←. Calcitonin inhibits the production of soft tissue calcification by parathyroid extract in the rat. Thyroxine has a similar effect, and combined treatment with the two hormones leads to a summation of their actions.

Drugs ←. In rats, the organ lesions produced by intoxication with holmium or indium chlorides, unlike the nephrocalcinosis produced by mercury, are completely prevented by calcitonin. The calcergy, induced by lead acetate i.v. + topical administration of polymyxin, is inhibited by calcitonin in the rat simultaneously with the hypercalcemia resulting from lead acetate administration.

The myocardial lesion, produced in rats as a consequence of the obstructive nephropathy caused by sulfa compounds is also inhibited by calcitonin.

The bone lesions characteristic of vitamin-A overdosage in the rat are prevented by calcitonin, although those elicited by various other techniques are not influenced by this hormone.

Renal Lesions ←. Calcitonin inhibits the metastatic calcification and the osteitis fibrosa induced by bilateral nephrectomy in the rat.

Parathyroid Hormone ← cf. also *Selye* G60,083/70, p. 413.

Tuchweber et al. G46,759/68; *Gabbiani et al.* G46,731/68; G46,730/68: Pretreatment with thyroxine or calcitonin inhibits the soft tissue calcification and osteitis fibrosa induced by parathyroid extract overdosage. In the event of concurrent administration, the effect of the two protective hormones is summed. Thyroxine retains its effect upon calcium metabolism in thyroparathyroidectomized or adrenalectomized but not in nephrectomized rats. The stress of restraint likewise prevents parathyroid overdosage, but the associated biochemical changes are different from those caused by thyroxine.

Drugs ←

Digitoxin ←. *Selye* PROT. 33541, 34074: In rats, PCN is highly efficacious in preventing digitoxin poisoning, even after parathyroidectomy, thyroparathyroidectomy, or concurrent treatment with propylthiouracil (PTU). No protection was obtained by thyroidectomy, parathyroidectomy or treatment with PTU,

thyroxine, parathyroid extract or calcitonin. Apparently, the goitrogenic effect of PCN plays no indispensable role in its catatoxic action.

Holmium, Indium ←. *Gabbiani & Tuchweber* G70,453/70: In rats, the organ lesions produced by toxic doses of holmium and indium chlorides—unlike the nephrocalcinosis elicited by HgCl_2 —are completely prevented by calcitonin.

Lead ←. *Gabbiani et al.* G46,731/68: In rats, calcitonin (but not thyroxine) inhibits the local calcergy induced by intravenous injection of lead acetate followed by topical administration of polymyxin and the hypercalcemia produced by a single injection of lead acetate.

Mercury ←. *Gabbiani & Tuchweber* G70,453/70: In rats, the organ lesions produced by toxic doses of holmium and indium chlorides—unlike the nephrocalcinosis elicited by HgCl_2 —are completely prevented by calcitonin.

Sulfa Drugs ←. *Fujita et al.* H2,733/68: In rats, calcitonin inhibits the myocardial lesions that occur as a consequence of the obstructive nephropathy after the administration of Na-sulfacetylthiazole (SAT).

Okano et al. H25,894/70: In rats, the calcification and necrosis of the aortic media induced by the "obstructive nephropathy" developing after injection of sodium sulfacytathiazole (SAT) can be prevented by parathyroidectomy, and to a lesser extent by calcitonin.

Vitamin A ←. *Clark et al. H5,009/68:* In rats, the bone lesions produced by vitamin-A overdosage were prevented by calcitonin, but those induced by various other techniques were not influenced, or actually aggravated.

Renal Lesions ←

Lefort et al. G46,725/67; Côté et al. G46,741/68: In rats, calcitonin inhibits the metastatic calcification and bone lesions induced by bilateral nephrectomy. In nephrectomized animals, thyroxine does not modify the changes induced by endogenous hyperparathyroidism consequent to bilateral nephrectomy. "Presumably, to be effective against soft-tissue calcification and bone resorption induced by parathyroid extract overdosage, thyroxine requires the presence of the kidney."

← PANCREATIC HORMONES

The pancreatic hormones affect resistance to various agents, mainly through their influence upon carbohydrate metabolism. It is interesting, however, that while the effect of insulin and surgically or drug-induced diabetes have been studied in connection with many toxicants, virtually no attention has been given to the possible corresponding effects of glucagon.

Steroids ←

Progesterone anesthesia is aggravated by insulin and prevented by epinephrine, presumably by virtue of the blood sugar changes produced by these hormones.

Nonsteroidal Hormones and Hormone-Like Substances ←

Thyroid feeding greatly increases mortality in rats on a diet containing desiccated pancreas. However, there is no proof that here pancreatic hormones play a role.

The toxicity of histamine, 5-HT, and of the anaphylactoidogenic agents that liberate these amines from mastocytes, is greatly influenced by pancreatic hormones. The anaphylactoid edema produced by dextran or egg-white in the rat is inhibited by alloxan diabetes and aggravated by insulin. The response to Cpd. 48/80 is less consistently influenced by these agents. In mice, sensitized with pertussis vaccine, alloxan also inhibits the response to 5-HT, histamine or anaphylaxis.

Steroids ← cf. also Selye G60,083/70, pp. 414—419.

Winter & Selye A35,658/41; Winter A36,333/41: Epinephrine increases, whereas insulin decreases, the resistance of the rat to the anesthetic action of progesterone.

Hydroxydione ← Carbutamide, Mouse: Rümke G69,768/63*

Nonsteroidal Hormones and Hormone-Like Substances ←

Thyroid Hormones ←. *Ershoff B24,883/48:* In immature female rats fed purified rations containing both pancreas and desiccated thy-

roid, mortality was high. Similar diets containing only pancreas or desiccated thyroid induced no comparable mortality.

Histamine and 5-HT ←. *Goth et al. C43,836/57:* In rats, alloxan diabetes inhibits the anaphylactoid edema produced by dextran or egg white; insulin aggravates it. Cpd. 48/80 is not influenced by these agents. "These results suggest a hitherto unrecognized role of insulin in certain types of inflammation and histamine release."

Adamkiewicz & Adamkiewicz C73,760/59: In rats, alloxan diabetes prevents the ana-

phylactoid reaction caused by dextran; insulin restores this reactivity.

Ganley & Robinson C66,305/59: In mice, sensitized with B. pertussis vaccine, alloxan inhibits the response to 5-HT and somewhat less to histamine and anaphylaxis.

Sanyal et al. C79,555/59: In rats, anaphylactoid edema produced by egg white is aggravated by insulin pretreatment.

Ganley D31,168/62: In mice, alloxan diabetes inhibits the sensitizing properties of

Bordetella pertussis vaccine as measured by challenge with histamine, 5-HT or anaphylaxis. This effect is reversed by insulin.

Insulin ←. Hasselblatt & Bastian C59,171/58: In mice, sensitivity to insulin convulsions is increased by thyroxine and even more markedly by tolbutamide.

Tolbutamide ← Tolbutamide, Dog: Charbon G76,685/61; Remmer et al. D19,894/64**

Drugs ←

Among the drug actions subject to regulation by pancreatic hormones, one of the most interesting is the previously mentioned response to **anaphylactoidogens**. Various antigen-antibody reactions are influenced in a similar way and since overdosage with sugars, cortisol or epinephrine also inhibit the anaphylactoid edema, it is assumed that the latter agents, like insulin and alloxan, act through their effect upon the blood sugar. Since these interrelations have been discussed at length in a previous monograph (*Selye G19,425/65*) they need not be discussed here in detail.

Barbiturate anesthesia can be markedly influenced by insulin but in a somewhat unpredictable manner. In mice, hexobarbital sleeping time is allegedly prolonged both by epinephrine and by insulin, whereas in rabbits, pentobarbital sleeping time is shortened by the same two hormones. In guinea pigs, hexobarbital sleeping time is also reduced by insulin and it has been postulated that here a direct effect upon both the CNS and upon hepatic detoxication may be involved. In mice, thiopental anesthesia is prolonged by alloxan diabetes, perhaps as a consequence of a deranged metabolic degradation of the barbiturate, but insulin fails to correct this effect.

Pancreatic hormones also appear to affect the toxicity of **digitalis alkaloids**. In dogs, pancreatectomy offers moderate protection against lethal doses of k-strophanthin; in rats, insulin enhances the cardiac action of this compound but not of its aglycon, strophanthidin.

The beriberi produced in pigeons by **vitamin-B₁** deficiency is aggravated by insulin, but only under certain circumstances. In rats, moderate alloxan diabetes does not significantly affect thiamine deficiency.

In rats pretreated with **vitamin D**, alloxan produces selective calcification of the Langerhans islets as a consequence of calciphylaxis.

Acetone ←

Hirschfelder & Maxwell 26,930/24: In rabbits, insulin fails to antagonize the toxic effects of ethanol or acetone.

Acetonitrile ←

Paal 22,603/30: Review of the literature and extensive personal studies on the acetonitrile test in mice and its use for the determina-

tion of thyroid hormone in human blood. Thyroidectomy does not increase the resistance of the mice to acetonitrile but diminishes the protective effect of thyroxine. Concurrent treatment with insulin also inhibits the prevention of acetonitrile toxicity by thyroxine.

Aminopyrine ← Alloxan + Insulin: Dixon et al. E35,705/63; Kato et al. F57,817/65

Anaphylactoidogens ← cf. also Selye G 46,715/68, pp. 104, 108, 177, 179, 184, 197.

Adamkiewicz & Langlois C 31,853/57: In rats, insulin sensitizes to the production of anaphylactoid edema by the systemic or intra-pedal injection of small doses of dextran. The sensitization manifests itself even despite cortisone treatment.

Adamkiewicz D 61,626/63: Review showing that "hyperglycemas resulting from over-dosage with sugars, cortisol, adrenaline, or from diabetes inhibit the anaphylactoid reactions; anaphylaxis, and the tuberculin reaction, but potentiate infections. Hypoglycemas resulting from fasting, insulin and adrenalectomy potentiate the anaphylactoid reactions, anaphylaxis, and the tuberculin reaction; but inhibit infections. The hypothesis is proposed that hyperglycemia inhibits certain antigen-antibody combinations; this results in an inhibition of hypersensitivity, but an aggravation of infection."

Sacra & Adamkiewicz F 49,352/65: In rats, the toxicity of Cpd. 48/80 is increased by insulin and diminished by glucose.

Aniline ← Alloxan + Insulin: Dixon et al. E 35,705/63

Aniline ← Alloxan + Orchidectomy + Methyltestosterone: Kato et al. F 57,817/65

Anticoagulants ← Tolbutamide, Rb, Man: Chaplin et al. D 99,463/58*

Anticoagulants ← Glucagon, Man: Koch-Weser G 73,494/70*

Barbiturates ←

Reinhard B 283/45: In mice, the hexobarbital sleeping time is prolonged by epinephrine or insulin.

Westfall B 31,306/46: In rabbits, pentobarbital sleeping time is shortened by epinephrine and insulin despite their opposite effect upon blood sugar.[This contradicts Reinhard B283/45 (H.S.).]

Holck B 42,745/48: In mice, neither epinephrine nor insulin altered significantly the fatal dose of hexobarbital given 20 min later.

Dixon et al. D 9,331/61: In alloxan diabetic rats, the ability of the hepatic microsomal fractions to inactivate hexobarbital, chlorpromazine or codeine in vitro is diminished and the sleeping time following hexobarbital injection in vivo prolonged. These effects can be reversed by insulin and roughly parallel the glycogen content of the liver. "Factors leading to severe depletion of hepatic glycogen will

probably affect the rate at which drugs are metabolized by the microsomes."

Shrotri et al. D 27,239/62: In guinea pigs, hexobarbital sleeping time is reduced by insulin. "A direct effect on the CNS as well as a role in the detoxification in liver are postulated."

Dixon et al. E 35,705/63: In alloxan-diabetic rats, "a depressed metabolism of hexobarbital and aminopyrine in vitro, an increased in vitro hydroxylation of aniline, and a prolonged in vivo effect of hexobarbital were evident. The O-dealkylation of codeine was unaffected by the chronic diabetic state. Insulin treatment returned the rate of metabolism of hexobarbital to normal levels but had no effect on aminopyrine metabolism. Metabolism of aniline was decreased below the normal rate after insulin treatment. Phenobarbital treatment of diabetic animals resulted in a stimulation of most of the drug-metabolizing enzyme systems studied. However, the hydroxylation of aniline by livers from diabetic rats treated with phenobarbital was decreased." A relationship between hepatic glycogen and drug-metabolizing enzyme activity is suspected.

Kato & Gillette F 57,817/65: The metabolism of aminopyrine and hexobarbital by hepatic microsomes of male rats is impaired by adrenalectomy, castration, hypoxia, ACTH, formaldehyde, epinephrine, morphine, alloxan or thyroxine. The metabolism of aniline and zoxazolamine is not appreciably decreased by any of these agents; in fact, hydroxylation of aniline is enhanced by thyroxine or alloxan. Apparently, the treatments impair mainly the sex-dependent enzymes. Accordingly, the corresponding enzymic functions of the hepatic microsomes of female rats are not significantly impaired by the agents which do have an inhibitory effect in males.

Vincent & Motin G 51,414/67: Description of a patient who recovered from severe combined intoxication with barbiturates and insulin.

Quevauviller & Podevin G 57,209/68: In mice, alloxan diabetes prolongs thiopental anesthesia by interfering with the metabolic degradation of the barbiturate. Insulin fails to correct this effect.

Weiner et al. H 24,942/70: In rats, glucagon, alloxan and starvation all increased hexobarbital sleeping time. This effect was markedly antagonized by insulin. Perhaps, cyclic AMP may be involved since theophylline greatly increases the action of glucagon. This synergism

also occurred in isolated, perfused rat livers and, hence, "inhibition of hexobarbital metabolism by cyclic AMP would appear to be mediated in the liver."

Amobarbital ← Insulin + Glucose, Rb: Maloney et al. 61,235/31*

Hexobarbital ← Insulin, Mouse: Reinhard B283/45*; Holck B42,745/48*, D28,543/49*

Hexobarbital ← Alloxan + Insulin: Dixon et al. D9,331/61*; Fouts G77,514/62; Dixon et al. E35,705/63

Hexobarbital ← Tolbutamide: Remmer G66,542/62*; Rümke et al. G74,669/60*; Kato et al. E47,494/64; Remmer et al. D19,894/64*, G66,868/65*; Remmer F90,864/67*

Bilirubin ←

Müller-Oerlinghausen & Schinke G79,199/70: In rats, the maximal transport capacity of the liver (T_m) for bilirubin is reduced in diabetes caused by alloxan or anti-insulin serum. "It is suggested that the reduced synthesis of UDP-glucuronic acid which has been found in former experiments in vitro is responsible for the impaired bilirubin excretion." The excretion of indocyanine green is likewise inhibited in experimental diabetes.

Bilirubin ← Tolbutamide, Dog: Singh et al. D6,799/61*

Caffeine ←

Labbé & Théodoresco 17,831/24: In dogs and rabbits, resistance to caffeine is somewhat increased by insulin but the results are not impressive.

Carbon Tetrachloride ←

Furukawa F71,711/65: In rats, hepatic steatosis produced by CCl_4 is inhibited by adrenalectomy and, to some extent, also by hypophysectomy. Corticoids restore the effect of CCl_4 after adrenalectomy; epinephrine does not, but it increases the effect of corticoids. STH does not counteract the effect of hypophysectomy. Alloxan diabetes inhibits CCl_4 -induced hepatic lipidosis.

Carcinogens ←

Dunning et al. A48,770/48: In rats, "the diabetic condition induced by alloxan shortened the life span of the affected individuals, thereby reducing both the percentage of rats

surviving long enough to develop benzpyrene sarcomas and the average latent period of those which did, but did not prevent or delay the malignant process in the rats surviving to the average time of occurrence for these neoplasms."

Salzberg & Griffin B68,802/52: In rats, hepatic carcinogenesis following treatment with 3'-Me-DAB is inhibited by alloxan diabetes.

Klärner & Klärner C45,812/58: In BAF₁ mice, the growth of urethan-induced pulmonary tumors is significantly inhibited by alloxan diabetes and exposure to heat, but only slightly affected by thyroxine and insulin.

Tinozzi & Pannella D54,092/61: In rats, alloxan diabetes largely prevents the induction of tumors by 20-methylcholanthrene.

Lacassagne & Hurst G78,530/69: In rats, tolbutamide (a hypoglycemic sulfonamide) accelerates, whereas diazoxide (a hyperglycemic sulfonamide) retards hepatoma formation after treatment with AAF. When the two compounds are given together, they nullify each other's actions.

Heuson G78,138/70: In rats, DMBA-induced mammary tumors appear to be influenced by insulin, both *in vivo* and *in vitro*. DNA synthesis in organ cultures of these carcinomas is stimulated by insulin. Large doses have a strong, probably direct stimulating effect on DMBA-induced neoplasms *in vivo*, whereas regression is noted in alloxan-diabetic rats.

Carisoprodol ← Tolbutamide: Kato et al. E47,494/64

Chlorpromazine ←

Wisniewski & Danysz G40,054/66: In rats, insulin administered simultaneously with chlorpromazine increases the potency and the brain concentration of the latter. "It can be supposed that insulin increases the velocity of the penetration of chlorpromazine across cell membranes in both directions. Hypoglycemia does not show any influence on this effect of insulin and it may be concluded that insulin acts directly on cell membranes."

Wisniewsky & Buczko G51,489/67: In rats, the depressive effect of chlorpromazine is decreased by alloxan and restored to normal by concurrent treatment with insulin.

Chlorpromazine ← Alloxan + Insulin: Dixon et al. D9,331/61*

Cholesterol ← cf. also Selye B40,000/50, p. 551; G60,083/70, pp. 414—419, 430.

Cholesterol ←

McGill et al. B32,954/49: In rabbits, cholesterol atherosclerosis is inhibited by alloxan diabetes contrary to the author's expectations.

Hamprecht G69,560/69: Review (7 pp., 153 refs.) on the mechanisms regulating cholesterol synthesis. A special section deals with the effect of thyroid hormones, steroids, epinephrine, norepinephrine and glucagon.

Wellmann et al. H9,536/69: In cholesterol-fed rabbits, alloxan aggravates the characteristic renal lesions.

Chromium ←

Zondek 36,326/14: In rabbits, the hypertension produced by uranium and mercury nephritis, unlike that of chromium nephritis, is counteracted by i.v. injection of a beef pancreas extract.

Cobalt ←

Avezzu C46,134/57: In rabbits, cobalt destroys the alpha cells, alloxan the beta cells, of the Langerhans islets, and hence, there exists a mutual antagonism between these two substances as regards the consequent metabolic effects also.

Codeine ← Alloxan + Insulin: Dixon et al. D9,331/61, E35,705/63

Digitalis ←

Freund A26,153/32: Studies on the effect of thyroidectomy or pretreatment with thyroxine or insulin upon the in vitro metabolic changes induced by digitalis compounds in the cat's heart.

Travis et al. C18,863/56: In dogs, pancreatectomy offers a slight but significant degree of protection against lethal doses of k-strophanthin. "This would appear to be related to the absence of insulin since hyperglycemia per se, does not afford any protection. Thus these results are in harmony with the concept that insulin facilitates the transport of glycosides having d-glucose as a terminal sugar in somewhat the same manner as it facilitates the transport of the simple sugar."

Adamkiewicz C97,998/61: In rats, insulin enhances the cardiac action of k-strophanthin but not of the aglycon strophanthidin.

Cohn et al. H26,723/70: In dogs, glucagon abolishes ouabain-induced arrhythmias. The mechanism of this anti-arrhythmic action could not be clarified but glucagon causes an im-

mediate rise, followed by a fall in serum potassium and this may have been involved.

Dyes ←

Müller-Oerlinghausen & Schinke G79,199/70: In rats, the maximal transport capacity of the liver (T_m) for bilirubin is reduced in diabetes caused by alloxan or anti-insulin serum. "It is suggested that the reduced synthesis of UDP-glucuronic acid which has been found in former experiments in vitro is responsible for the impaired bilirubin excretion." The excretion of indocyanine green is likewise inhibited in experimental diabetes.

Dye (BSP) ← Tolbutamide, Rb: Hasselblatt et al. G77,523/62*

Dye (BSP) ← Tolbutamide + Ethionine, Mouse: Fujimoto et al. G30,289/65*

Ethanol ←

Hirschfelder & Maxwell 26,930/24: In rabbits, insulin fails to antagonize the toxic effects of ethanol or acetone.

Hiestand et al. B78,576/53: In mice, alloxan diabetes and epinephrine increase, whereas insulin decreases, sensitivity to lethal doses of ethanol.

Hirvonen et al. G59,966/68: In rats, moderate chronic ethanol intoxication causes hypertrophy of the adrenal glomerulosa. This effect is inhibited by insulin. On the other hand, the ethanol-induced activation of the fasciculata is actually enhanced by insulin.

Ethanol ← Alloxan, Mouse: Hiestand et al. B78,576/53*

Ethanol ← Insulin + Glucose, Dog: Greenberg A48,342/42*; Sammalisto G76,362/62*

Hexadimethrine ←

Kovács & Szijj F96,892/68: In rats, insulin increases sensitivity to hexadimethrine-induced pituitary necrosis; alloxan fails to affect it.

Lathyrogens ←

Franchimont et al. D13,136/61: In rats, osteolathyrysm produced by AAN is aggravated by 5-HT, whereas glucagon does not modify it significantly.

van Caruwenberge & Lefebvre G58,189/64: In rats, osteolathyrysm produced by AAN is not influenced by glucagon.

Meprobamate ← Tolbutamide: Kato et al. E47,494/64

Mercury ←

Zondek 36,326/14: In rabbits, the hypertension produced by uranium and mercury nephritis, unlike that of chromium nephritis, is counteracted by i.v. injection of a beef pancreas extract.

Methampyrone ← Tolbutamide: Remmer *F*90,864/67

Methylaminoantipyrine ← Tolbutamide: Remmer *G*6,542/62

Monomethylaminoantipyrine ← Tolbutamide: Remmer et al. *D*19,894/64

Morphine ←

Wiśniewski *E*32,005/63: In rabbits, insulin increases the analgesic action of morphine and dolantin.

Pentylenetetrazol ←

Waltregny & Mesdjian *F*78,025/66: In cats, insulin hypoglycemia raises sensitivity to pentylenetetrazol convulsions.

Peptone ←

Barral et al. *8*,860/32: In guinea pigs, anaphylactic and peptone shocks are aggravated by insulin and diminished by glucose.

Pesticides ←

DuBois et al. *B*3,089/47: In rats, both insulin and hypophysectomy antagonize the hyperglycemic effect of ANTU but do not prolong survival.

Dieldrin ← Tolbutamide: Matsuura et al. *G*74,472/68

Picrotoxin ← Insulin: Holck *D*28,543/49*

Salicylates ←

Wiśniewski & Zarebski *F*85,977/67; *F*96,973/68: In mice, insulin greatly increases the analgesic effect of Na-salicylate and its concentration in the brain, heart and skeletal muscle. Alloxan has an opposite effect.

Strychnine ← Tolbutamide: Kato et al. *E*47,494/64

Thiouracil ←

Pyatnitskaya *C*43,809/56: In rats, the fatty degeneration of the liver produced by thiouracil is prevented by conjoint administration of insulin and glucose.

Thioacetamide ←

Georgii et al. *C*69,388/59: In rats, the hepatic lesions produced by chronic treatment with thioacetamide are at first inhibited and later aggravated by concurrent administration of an antidiabetic sulfanil urea preparation (*D* 860, artosin, tolbutamide).

Toluene Diisocyanate ←

Thompson & Scheel *G*55,229/68: In rats, the toxicity of toluene diisocyanate is diminished by alloxan and increased by insulin or pertussis vaccine. Yet, other evidence suggests that the pulmonary changes produced by this drug are not due to an allergic reaction but to direct chemical damage.

Uranium ←

Zondek 36,326/14: In rabbits, the hypertension produced by uranium and mercury nephritis, unlike that of chromium nephritis, is counteracted by i.v. injection of a beef pancreas extract.

Vitamin-B Complex ← cf. also *Selye* *C*92,918/61, p. 231.

Chahovitch 26,462/25: In pigeons, insulin aggravates the already manifest symptoms of incipient thiamine deficiency.

Chahovitch 26,685/25: In pigeons, insulin pretreatment retards the development of beriberi on a thiamine-deficient diet.

Baglioni & Console 45,284/34: In pigeons on a thiamine-deficient diet, the development of beriberi is delayed by daily treatment with insulin, but only under certain experimental circumstances. The extensive literature on the effect of insulin upon beriberi is reviewed.

Janes & Brady 98,541/47; *B*23,359/48: In rats, alloxan diabetes does not significantly alter the thiamine-deficiency syndrome.

Vitamin D ←

Kodousková et al. *D*69,797/63: In rats pretreated with vitamin D, alloxan causes calcification of the Langerhans islets as a manifestation of calciphylaxis.

Zinc ←

Kamikubo *D*7,362/59: In rats, alloxan decreased the comparatively high zinc content of Yoshida's ascites tumor.

Varia ←

Störtebecker 76,398/39: Review of the early literature (1924—1937) on the effect of the pancreas upon resistance to various drugs.

Selye G70,480/71: In rats, tolbutamide protects against intoxication with dioxathion,

parathion, hexobarbital, progesterone (anesthesia), indomethacin but not against digitoxin, nicotine, zoxazolamine, DHT or the infarctoid cardiopathy produced by fluorocortisol + Na_2HPO_4 + corn oil.

Microorganisms, Vaccines and Parasites ←

It is a well-known fact that both pancreatic and alloxan diabetes increase sensitivity to a great variety of bacteria, including *Mycobacterium tuberculosis*, *pneumococcus*, *staphylococcus*, *streptococcus*, *perfringens* and many others.

Alloxan diabetes also aggravates the course of infestation with various parasites, especially, fungus infections.

In mice, insulin decreases resistance to endotoxins allegedly because the hypoglycemic state interferes with defense against the stressor effect of these lipopolysaccharides.

Bacteria and Vaccines ←

Bordetella Pertussis ←. *Ganley & Robinson* C66,305/59: In mice, sensitized with *B. pertussis* vaccine, alloxan inhibits the response to 5-HT and somewhat less to histamine and anaphylaxis.

Ganley D31,168/62: In mice, alloxan diabetes inhibits the sensitizing properties of *B. pertussis* vaccine as measured by challenge with histamine, 5-HT or anaphylaxis. This effect is reversed by insulin.

Clostridium Welchii ←. *Wishart & Pritchett* 12,285/20: In dogs, partial pancreatectomy, conducive to severe glycosuria, fails to diminish resistance to infection with *C. welchii*.

Escherichia Coli ←. *Krizek & Davis* F14,734/64: In rats given alloxan and maintained with insulin, the proliferation of *E. coli* injected s.c. was not greatly altered.

Mycobacterium Tuberculosis ←. *Schäfer* B99,955/54: Monograph (127 pp., numerous refs.) on the role of endocrine factors in tuberculosis. Special sections are devoted to the hormones of the thyroid, parathyroid, thymus, adrenals, pancreas and gonads.

Renovanz C78,772/59: In guinea pigs, the course of experimental tuberculosis was not markedly influenced by ACTH, tolbutamide derivatives or antithyroid treatment with perchlorates.

Schäfer & Greuel D54,900/62: In guinea pigs, the oral antidiabetic, tolbutamide has a deleterious effect upon the development of experimental tuberculosis.

Dobrev G23,362/64: In rabbits, alloxan diabetes aggravates the course of experimental tuberculosis and diminishes the allergic response to tuberculin.

Pneumococcus ←. *Drachman et al.* F81,617/66: In rats, alloxan diabetes increases susceptibility to experimental Type 25 pneumococcal pneumonia presumably through a depression in phagocytosis.

Staphylococcus, Streptococcus ← cf. also *Selye* G60,083/70, p. 418. *Lauber* 9,102/32: Observations on the effect of insulin upon streptococcal and staphylococcal infections in mice.

Schultz & Rose B31,347/39: "Guinea pigs treated with maximum tolerated doses of protamine insulin and subjected to chronic, hemolytic streptococcal, focal infection develop nonpurulent carditis. This susceptibility to cardiac damage during infection is probably associated with the altered metabolic activity incident to insulin treatment."

Bóbr G30,418/65: In mice, alloxan diabetes raises susceptibility to *Staphylococcus pyogenes*.

Welchia Perfringens ←. *Adamkiewicz et al.* F99,983/67: Mice rendered diabetic by alloxan are sensitive to doses of washed *Welchia perfringens* which are innocuous for normal controls.

Parasites ←

Mucormycosis ←. *Elder & Baker* C12,831/56: In rabbits, alloxan diabetes aggravates the course of pulmonary mucormycosis following intratracheal inoculation of *Rhizopus* spores.

Trypanosoma Equiperdum ←. *Ewing et al. B50,244/50:* In mice infected with *T. equiperdum*, severe hypoglycemia develops and both alloxan and glucose exert an immediate analeptic effect.

Varia ←. *Sheldon & Bauer D46,962/62:* Review on the role of predisposing factors, particularly alloxan diabetes and ACTH-treatment, upon various fungus infections.

Bacterial Toxins ← cf. also Selye E5,986/66, p. 82.

Pieroni & Levine G68,105/69: In mice, insulin increases mortality produced by endotoxin. "This result is consistent with the thesis that there is a reciprocal relationship between the glycemic state of a host and its susceptibility to a wide variety of stressor agents."

Immune Reactions ←

We have already mentioned that insulin increases, whereas alloxan diabetes decreases, the anaphylactoid reaction as well as various antigen-antibody responses in different species. Similar effects have been noted in connection with the response to histamine and 5-HT in normal or pertussis sensitized animals. Let us add here that in guinea pigs, anaphylactic and peptone shock are aggravated by insulin and diminished by glucose. Alloxan also desensitizes the guinea pig to tuberculin and this effect is inhibited by insulin.

Barral et al. 8,860/32; 8,858/32: In guinea pigs, anaphylactic and peptone shocks are aggravated by insulin and diminished by glucose.

Cornforth & Long B77,176/53: In guinea pigs sensitized to tuberculin, single s.c. injections of ATP prevent desensitization by alloxan, cortisone and dihydroascorbic acid. Single s.c. injections of insulin do not in themselves influence sensitivity but prevent desensitization by alloxan and cortisone. Single s.c. injections of STH depress tuberculin sensitivity and synergize the action of cortisone or alloxan.

Long & Shewell G71,833/54: In guinea pigs, allergic hypersensitivity to BCG is increased by thyroxine or insulin. Partial pancreatectomy

has no effect on sensitivity by itself but prevents the action of thyroxine, although not that of insulin.

Long & Shewell G71,832/55: In guinea pigs, thyroxine increases immunity as judged by the local response to diphtheria toxin injected intradermally and of circulating antitoxin after immunization with diphtheria toxoid. Partial pancreatectomy prevents this effect of thyroxine.

Ganley & Robinson C66,305/59; Ganley D31,168/62: In mice, alloxan diabetes inhibits the sensitizing properties of *Bordetella pertussis* vaccine as measured by challenge with histamine, 5-HT or anaphylaxis. This effect is reversed by insulin.

Stressors ←

There is no conclusive evidence to suggest that resistance to ionizing rays can be significantly affected by pancreatic preparations. However, in rats, both insulin and carbutamide diminish resistance to hypoxia.

In cats, dogs and chickens, insulin delays the appearance of the shivering reflex upon exposure to cold, whereas glucose reinstalls it. Combined treatment with cold and insulin elicits a state simulating hibernation. Both insulin and alloxan diminish resistance to cold in various species; however, in guinea pigs, insulin allegedly increases resistance to heat stroke.

Combined treatment with insulin + glucose increases the resistance of the rat to trauma in the Noble-Collip drum.

Ionizing Rays ←

Cavallot & Einaudi C30,084/56: In guinea pigs, resistance to whole body X-irradiation is increased by treatment with an insulin-free pancreatic extract.

Gordyeva C97,407/60: In rats, resistance to total body X-irradiation is increased by glucose but additional administration of insulin is of no further advantage.

Hypoxia and Hyperoxygenation ←

Campbell A14,903/37: In rats exposed to six atmospheres of oxygen in a pressure chamber, subsequent decompression is better tolerated at low than at high external temperatures. At 24°C, the following substances, administered s.c., enhance oxygen poisoning: thyroxine, dinitrophenol, ac-tetrahydro- β -naphthylamine, epinephrine, pituitary extract (posterior lobe), insulin, and eserine + atropine. These doses in themselves are harmless.

Fister C97,077/59: In the rat, both insulin and carbutamide lower resistance to hypoxia.

Kawashima & Ueda F68,970/66: In rats, insulin sensitizes to hypoxia. This effect is inhibited by urethan.

Cold ←

Cassidy et al. 24,604/25: In cats and dogs, insulin hyperglycemia abolishes the shivering reflex elicited by exposure to cold. Glucose

causes its reappearance. Combined treatment with cold and insulin elicits a state simulating hibernation in cats and dogs.

Cassidy et al. 26,459/26: In chickens, insulin delays the appearance of shivering upon exposure to cold until the blood sugar rises.

Tullio 22,671/30: In rabbits, exposure to cold decreases the blood sugar, and insulin hypoglycemia decreases resistance to cold.

Poe & Davis D27,155/62: In rats, alloxan diabetes diminishes resistance to cold.

Poe et al. E21,412/63: In rats, alloxan diabetes diminishes resistance to cold but some adaptation to low temperature is possible even during the diabetic stage.

Heat ←

Grazia & Sardo 27,853/34: In guinea pigs, insulin increases resistance to heat stroke.

Trauma ←

Triner et al. D65,801/63: In rats, treatment with insulin + glucose increases resistance to trauma in the Noble-Collip drum.

Varia ←

Ouzelatz C36,618/57: In rats, insulin aggravates the production of gastric ulcers by pylorus ligature.

Hepatic Changes ←

In rats, alloxan and various antidiabetics can produce severe, often necrotizing, hepatic lesions.

Scharf et al. F69,957/66: In rats, chronic treatment with methylthiouracil or paroxypropion produces essentially similar hepatic lesions. T2 reduces liver glycogen and the size of the hepatocytes. Single large doses of alloxan cause severe necrotizing lesions followed by cell proliferation. Concurrent treatment with methylthiouracil inhibits the allo-

xan-induced hepatic lesions and diminishes mortality.

Klatskin G65,221/69: Review (103 pp., 809 refs.) on toxic and drug-induced hepatitis with special sections on the hepatotoxic effect of testoids, corticoids, thioureas, luteoids, folliculoids and oral antidiabetics.

Hepatic Enzymes ←

For the literature concerning the effect of pancreatic hormones upon the basic levels of hepatic TPO, TKT, GOT, GPT, SDH, TDH cf. Abstracts.

TPO, TKT ←

Schor & Frieden C57,994/58: In the rat, insulin can induce TPO activity, and its effect is only partly inhibited by adrenalectomy. In the intact rat, the effect of insulin and tryptophan, or insulin and cortisone, are additive. Possibly, "hormonal induction may be a form of substrate induction in that certain hormones might affect the availability of typtophan for the enzyme-forming system."

Finch et al. G71,208/69: In senescent mice, the induction of hepatic TKT by exposure to cold is delayed in comparison with young mice. Corticosterone and insulin are equally effective in this respect in mice of both age groups.

SDH, TDH ←

Freedland & Avery G67,766/64: In the rat, the TDH and SDH activity of liver homogenates was increased by high-protein diets, alloxan diabetes, or cortisol. Factors affecting the activity of TDH caused a proportional change in SDH suggesting that both of these activities may be due to a single protein. The SDH activity was decreased by adrenalectomy or hypophysectomy. Adrenalectomy had no effect upon the response of this enzyme to protein feeding, whereas, after hypophysectomy, this response was diminished.

Ishikawa et al. F41,763/65: In alloxan-diabetic rats, the SDH and TDH levels of the hepatic microsomes are greatly enhanced. SDH was readily induced by cortisol in the diabetic, but not in the normal rat. The effects of actinomycin S, STH, and starvation upon SDH have also been studied in intact, hypophysectomized, adrenalectomized and thyroidectomized rats. It is concluded that "serine dehydratase activity in the liver plays an important role in the production of pyruvate as a starting material for gluconeogenesis."

GPT, GOT ←

Rosen et al. C50,741/58: In rats treated with cortisol, cortisone or prednisone for 1 week, there was an increase in hepatic GPT but not in GDT. DOC had no such effect. Hypophysectomy or adrenalectomy did not prevent this action of cortisone. STH, testosterone or insulin failed to alter GPT activity nor did they influence its stimulation by cortisol.

Rosen et al. C71,414/59: Marked increases in GPT activity were observed in the livers of rats given cortisol, cortisone, 9a-fluorocortisol,

prednisone, 6a-methylprednisolone, 9a-fluoro-21-desoxy-6a-methylprednisolone or ACTH, whereas two nonglucocorticoid cortisol derivatives, 11-epicortisol and 9a-methoxycortisol were inactive. STH, testosterone and insulin caused no significant change in GPT by themselves nor did they modify the action of cortisol. On the other hand, large doses of estradiol and thyroxine caused a moderate increase in GPT activity but when injected simultaneously with cortisol, they appeared to interfere with its action as did progesterone. Adrenalectomy slightly diminished or failed to affect the GPT-inducing activity of cortisol, whereas hypophysectomy caused a rise in GPT activity and augmented the effect of cortisol.

Rosen et al. G66,496/59: In the rat, cortisol, cortisone and prednisone cause a 6—13 fold increase in hepatic GPT activity. This effect was directly related to the protein content of the ration. In alloxan diabetic rats, the rise in this enzyme activity was equivalent to that obtained by cortisol or high-protein diets and could be inhibited by insulin. Adrenalectomy diminished but did not abolish the rise in GPT activity obtained by feeding high-protein diets. Thus, the initiation of enzyme synthesis by dietary protein is not mediated exclusively through the adrenals.

Other Enzymes ←

Schweppé & Jungmann H15,266/69: The ability of rat liver microsomes to synthesize cholesterol palmitate, oleate and linoleate in vitro is increased by the addition of thyroxine or glucagon to the incubation medium. Testosterone increases cholesterol palmitate and oleate formation. 17 β -Estradiol stimulates mainly oleate synthesis.

Harada et al. H15,156/69: The acetyl-CoA-synthetase activity of the rat liver increases 2—3-fold during alloxan diabetes, fasting, or high-fat diet feeding.

Kato & Takahashi H11,853/69: "The magnitude of increase in the activities of microsomal drug-metabolizing enzymes and NADPH-linked electron transport system in the alloxan diabetic rats was greater than in normal rats, in contrast, the magnitude of increase in the thyroxine-treated rats was smaller than in normal rats."

Müller-Oerlinghausen et al. G64,175/69: Hepatic tissue of mice which had been injected with tolbutamide, synthesizes an increased

amount of glucuronide when incubated in vitro with o-aminophenol. Insulin given at a dose causing a similar degree of hypoglycemia is much less effective in enhancing glucuronide synthesis. Adrenalectomy diminishes the formation of o-aminophenol glucuronide, despite hypoglycemia. However, adrenalectomized mice given cortisone again respond with increased glucuronide synthesis following tolbutamide.

Shou et al. H15,277/69: In the rat, the hepatic methionine adenosyl transferase activity was not much influenced by glucagon, but during alloxan diabetes it increased considerably. Combined treatment with alloxan and triamcinolone resulted in an additive effect. The response to alloxan could be prevented and even reversed by insulin or adrenalectomy. In normal rats, insulin caused no consistent increase.

← EPINEPHRINE AND NOREPINEPHRINE

Even before Walter Cannon put forth his classic concept of the "emergency reaction," it had been realized that the adrenal medulla plays an important part in defense, especially through its effect upon the cardiovascular system. In a sense, the secretion of vasopressor catecholamines into the blood stream complements the protective and adaptive effects of the sympathetic nervous system. On the other hand, we know very little about the possible direct effects of these hormones upon detoxication mechanisms apart from the fact that they may influence these by altering the liver glycogen and blood sugar concentrations.

Steroids ←

In the rat, epinephrine increases, whereas insulin decreases the anesthetic effect of progesterone. Also in rats, epinephrine and norepinephrine produce eclampsia-like manifestations following pretreatment with DOC + NaCl.

Nonsteroidal Hormones and Hormone-Like Substances ←

In mice, pretreatment with epinephrine increases resistance to this catecholamine in a rather specific manner.

The diabetogenic action of alloxan is diminished by epinephrine in the rabbit.

In dogs, many of the changes produced by thyroid preparations are abolished by sympathetic blockade and increased by epinephrine and norepinephrine.

The toxicity of histamine is as markedly increased by complete sympathetic blockade as it is by total adrenalectomy in the rat. Epinephrine counteracts the increased susceptibility to histamine, but not to several other stressor agents. It appears that the adrenergic system is the first line of defense against certain stressors (e.g., histamine, endotoxin), whereas resistance to others (e.g., formalin, tourniquet shock) is more dependent upon glucocorticoids.

Steroids ← cf. also Selye G60,083/70, pp. 331, 358, 360.

Winter & Selye A35,658/41; Winter A36,333/41: Epinephrine increases, whereas insulin decreases, the resistance of the rat to the anesthetic action of progesterone.

Pellanda C7,961/55: In rats pretreated with DOC and NaCl, epinephrine or norepinephrine produces an eclampsia-like syndrome.

Cortisol ← Epinephrine: Kumagai et al. C57,345/58

Steroids ← Norepinephrine, Cattle: Cooper et al. D20,337/62

17 α -Hydroxyprogesterone ← Epinephrine, Cattle: Cooper et al. D20,338/62

Nonsteroidal Hormones and Hormone-Like Substances ← cf. also Selye C92,918/61, pp. 112, 121; G60,083/70, pp. 358—362.

Brewster Jr. et al. C11,771/56: In dogs, the physiologic changes produced by thyroid extract are abolished following sympathetic blockade. The inotropic, chronotropic and calorogenic effects of epinephrine and norepinephrine are increased by thyroid feeding. "It is concluded that there is a dynamic interrelationship between the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings."

Carrasco-Formiguera & Escobar B19,877/48: In rabbits, epinephrine i.m. inhibits the diabetogenic action of **alloxan**.

Gasic B17,561/47: In mice, pretreatment with **epinephrine** increased resistance to this catecholamine but not to formalin. Apparently, at least under these conditions, cross-resistance does not occur.

Krauczak & Brodie H25,296/70: In rats, complete blockade of sympathetic function can be achieved by demedullation combined with reserpine-like agents (depleting catecholamine stores), bretylium-like agents (preventing nerve impulse from releasing catecholamines)

or ganglioplegics. Following such total sympathetic blockade, mortality from histamine or endotoxin is as markedly increased as by adrenalectomy. Pretreatment with epinephrine alone counteracts the increased lethality of endotoxin and **histamine** after sympathetic blockade. Cortisone pretreatment only partially corrects the sensitization by adrenalectomy, whereas cortisone + epinephrine offers complete protection against these agents. Presumably, sympathetic stimulation is "the first line of defense against the vasomotor disturbance elicited by endotoxin and histamine." The lethal effect of formalin or tourniquet shock is likewise greatly increased by adrenalectomy but, in contrast to that of endotoxin and histamine, it cannot be increased by sympathetic blockade. Furthermore, cortisone alone counteracts the toxicity of these stressors in adrenalectomized rats. Apparently "formalin and tourniquet shock is initiated by a mechanism which differs from that elicited by histamine and endotoxin and does not primarily involve the sympathetic system."

Drugs ←

The **anaphylactoid** edema produced in rats by egg-white can be prevented by epinephrine or norepinephrine, but not by isoproterenol. The gastric hemorrhages elicited by polymyxin (another anaphylactoidogen) are even more effectively prevented by epinephrine than by various antihistamines.

In guinea pigs, epinephrine injected on awakening from **barbiturate** anesthesia produced a return of sleep. This effect could be duplicated by glucose, lactate or glutamate in intact animals but after adrenalectomy only epinephrine was effective. In mice, epinephrine also prolongs the hypnotic effect of various barbiturates, although allegedly thiopental and barbital anesthesia is mildly reduced by it, under certain circumstances, perhaps because epinephrine (unlike norepinephrine) enhances the penetration of barbital into the brain. In any event barbital and epinephrine (but not norepinephrine) may cause very peculiar neurologic manifestations — associated with ataxia, incoordination and loss of righting reflex — at doses at which barbital alone has no such effect.

In rabbits, pentobarbital sleeping time is shortened by epinephrine, but if administered just after awakening from thiopental anesthesia, epinephrine reinduces sleep; yet, epinephrine (unlike norepinephrine) causes rapid awakening if given to rabbits during thiopental anesthesia.

Carbon tetrachloride given simultaneously with epinephrine to the dog often leads to fatal ventricular fibrillation. In rats, epinephrine or norepinephrine fails to potentiate the hepatotoxic effect of CCl_4 and, in isolated perfused rat livers, the hemodynamic effects of norepinephrine are increased by CCl_4 . On the other hand, in mice the hepatotoxicity of CCl_4 has been claimed to be considerably increased by concurrent administration of either epinephrine or norepinephrine.

In dogs, epinephrine injected during chloroform anesthesia readily produces collapse and death. Pretreatment with epinephrine has no such effect, indeed it may protect the dog against subsequent combined treatment with chloroform and epinephrine. The chloroform-epinephrine collapse can be prevented in dogs by lithium carmine or induced hypothermia.

The muscular paralysis produced by curare derivatives can be inhibited by epinephrine in several species.

Various observations suggest that at least under certain circumstances norepinephrine may increase the effect of digitalis derivatives.

The toxicity of ganglioplegics (e.g., hexamethonium) is counteracted by epinephrine in the guinea pig. On the other hand, tetraethylammonium may considerably sensitize the dog to the pressor effect of epinephrine and other vasopressor agents. In rabbits, combined treatment with epinephrine and tetraethylammonium may also result in dangerous intoxication.

There is some evidence that in rats and dogs, epinephrine offers some protection against mescaline intoxication.

The head and neck edema induced by paraphenylenediamine is moderately inhibited by epinephrine.

In mice, pentylenetetrazol convulsions can be inhibited by combined administration of norepinephrine and 5-HT into certain regions of the brain. In one-day old chicks in which the blood-brain barrier is still incompletely formed, epinephrine (as well as 5-HT or histamine) prevent pentylenetetrazol convulsions and produce sleep.

Picrotoxin convulsions are also inhibited by intracerebral administration of epinephrine or 5-HT in mice.

In various species, reserpine intoxication is counteracted by epinephrine.

In rabbits, concurrent treatment with sparteine and epinephrine causes cardiac and hepatic lesions which are not obtained at comparable dose levels by either agent alone.

Epinephrine offers considerable protection against strychnine convulsions in frogs, guinea pigs and mice.

In cholesterol-fed rabbits, the anti-atheromatous action of Tween 80 is inhibited by norepinephrine.

It has been claimed that, in vitamin-D deficient rats, the healing of rickets can be initiated by epinephrine, but these observations require confirmation. On the other hand, the production of cardiovascular calcification by DHT is enhanced by norepinephrine in the rat. The progeria-like syndrome produced by chronic treatment with small doses of DHT in rats is not influenced by epinephrine. However, a single large dose of this catecholamine often causes calcifying mural ball valve thrombi in the left atrium of rats pretreated with large doses of DHT (or parathyroid extract).

Acetonitrile ←

Paal 22,603/30: In mice, acetonitrile resistance is not consistently influenced by posterior pituitary extract (hypophysin), a

folliculoid preparation (progynon), or epinephrine.

Dessau 34,845/35: In rats, adrenalectomy decreases resistance to acetonitrile. Resistance

can be slightly restored by adrenocortical transplants, but not by the adrenocortical extract tested or by epinephrine.

Allyl Alcohol ←

Strubel et al. G80,282/70: In rats, norepinephrine did not augment the hepatotoxicity of CCl_4 or allyl alcohol at doses of 0.25 mg/kg or less. However, at the dose of 1 mg/kg, at which norepinephrine itself causes liver damage, it potentiates the hepatotoxicity of these agents. Earlier claims that CCl_4 causes liver damage only through the massive liberation of endogenous catecholamines could not be confirmed.

Aminopyrine ← *Norepinephrine + Phenoxybenzamine:* Dixon et al. *G11,757/64*

Amitriptyline ←

Nymark & Rasmussen G42,054/66: In rabbits, norepinephrine offered no considerable protection against the ECG changes produced by amitriptyline.

Anaphylactoidogens ← cf. also *Selye B40,000/50, p. 758; G46,715/68, pp. 177, 178, 181, 187.*

Clark & MacKay B36,925/49: In rats, the anaphylactoid edema produced by egg white i.p. is prevented by epinephrine or norepinephrine s.c.; isoproterenol is ineffective.

Moreno & Brodie D20,261/62: In rats, the gastric hemorrhages that occur 2 hrs after polymyxin s.c. are more effectively prevented by epinephrine than by various antihistamines (cyproheptadine, chlorpheniramine, pyrilamine). At very high doses, chlorpromazine and dibenzyline were also effective but anticholinergic drugs and antacids were not. Presumably, lesions were due to gastric vascular changes without involvement of the secretory mechanism.

Adamkiewicz D61,626/63: Review showing that "hyperglycemics resulting from overdosage with sugars, cortisol, adrenaline, or from diabetes inhibit the anaphylactoid reactions; anaphylaxis, and the tuberculin reaction; but potentiate infections. Hypoglycemics resulting from fasting, insulin and adrenalectomy, potentiate the anaphylactoid reactions, anaphylaxis, and the tuberculin reaction; but inhibit infections. The hypothesis is proposed that hyperglycemia inhibits certain antigen-antibody combinations; this results in an inhibition of hypersensitivity, but an aggravation of infection."

Aniline ← *Norepinephrine + Phenoxylbenzamine:* Dixon et al. *G11,757/64*
Antibiotics ← cf. *Selye G60,083/70, pp. 358, 361.*

Anticoagulants ←

Jacques G70,979/68: Review (30 pp., 13 refs.) on the "hemorrhagic stress syndrome" that is produced in various mammals treated with indirect anticoagulants (e.g., phenindione, dicoumarol) and then exposed to stress or treated with DOC, ACTH, or STH. Conversely, cortisone, epinephrine, ephedrine and adrenochrome inhibit this syndrome.

Arsenic ←

Hanzlink & Karsner 10,286/20: In guinea pigs, epinephrine can prevent true anaphylactic shock but not the anaphylactoid shock produced by peptone, dextrin or agar. The arsphenamine-induced disturbances (which have been regarded by some as anaphylactoid) are diminished by epinephrine, presumably as a consequence of its circulatory action.

Barbiturates ←

Dog

Werle & Lentzen A28,007/38: In dogs and rabbits, various vasoactive substances (epinephrine, histamine, vasopressin, kallikrein) tend to prolong the anesthetic effect of promnarcon and hexobarbital.

Rolf & Campbell H18,467/69: In dogs, anesthesia by various thiobarbiturates sensitizes for the production of cardiac arrhythmias by epinephrine.

Hexobarbital ← *Epinephrine, Dog:* *Dallemane A47,748/41**

GUINEA PIG

Lamson et al. B89,712/52: In guinea pigs, epinephrine injected i.p. on awakening from barbiturate anesthesia produced a return to sleep. A similar effect was caused by glucose, lactate, or glutamate. However, in adrenalectomized animals, only epinephrine was effective.

Hexobarbital ← *Epinephrine, Gp:* *Lamson et al. C14,547/51**

MOUSE

Reinhard B283/45: In mice, the hexobarbital sleeping time is prolonged by epinephrine or insulin.

Holck B42,745/48: In mice, neither epinephrine nor insulin altered significantly the fatal dose of hexobarbital given 20 min later.

Fastier D95,950/56: In mice, 5-HT considerably potentiates the hypnotic effect of cyclobarbital and chloral hydrate. However, this property is not very specific, since bufotinine, tryptamine, histamine, and epinephrine likewise prolong cyclobarbital hypnosis. Literature on numerous other drugs which prolong barbiturate anesthesia is cited. "It therefore seems possible that the ability of 5-HT to prolong hypnosis may be due to a relatively unspecific, vascular effect."

Pradhan et al. C13,632/56: In 3 strains of mice, urethan sleeping time was greatly increased by epinephrine and norepinephrine. Phenobarbital sleeping time was only mildly increased by epinephrine.

Komiya et al. C21,326/56: In mice, thiopental anesthesia is reduced in severity, but not in duration, by epinephrine. Barbital anesthesia was slightly reduced by norepinephrine but not by epinephrine. Unpublished experiments suggest that ACTH and glucocorticoids shorten the duration of barbital anesthesia in mice.

Holtz et al. C76,300/58: In mice just awakening from hexobarbital anesthesia, sleep is reinduced by norepinephrine but not by epinephrine.

Kato C78,047/59: In mice, the prolongation of pentobarbital or hexobarbital sleeping time by 5-HT (administered in the form of its precursor 5-HTP which penetrates the brain barrier more readily) is inhibited by DOPA; the latter presumably acts as a precursor of norepinephrine.

Mazel & Bush D4,194/61: In mice, the penetration of barbital into the brain and the resulting anesthesia are enhanced by epinephrine but not by norepinephrine.

Fouts D43,347/62: Repeated injections of epinephrine i.p. increase the hexobarbital- and chlorpromazine-destroying effect of hepatic microsomal fractions in the rat.

Ellinwood & Prange E39,187/64: In mice, high doses of epinephrine prolonged sleeping time in themselves and potentiated the effect of thyroid feeding. The prolongation of pentobarbital sleeping time by epinephrine may be due to depletion of hepatic glycogen which interferes with hepatic microsomal-drug metabolism.

Kato & Gillette F57,817/65: The metabolism of aminopyrine and hexobarbital by hepatic microsomes of male rats is impaired by

adrenalectomy, castration, hypoxia, ACTH, formaldehyde, epinephrine, morphine, alloxan or thyroxine. The metabolism of aniline and zoxazolamine is not appreciably decreased by any of these agents; in fact, hydroxylation of aniline is enhanced by thyroxine or alloxan. Apparently, the treatments impair mainly the sex-dependent enzymes. Accordingly, the corresponding enzymic functions of the hepatic microsomes of female rats are not significantly impaired by the agents which do have an inhibitory effect in males.

Vizet F77,760/67: In mice, combined treatment with barbital and epinephrine causes "spectacular neurologic modifications," with ataxia, muscular incoordination and loss of righting reflex, at dose levels at which barbital alone has no such effect. Norepinephrine does not markedly influence barbital intoxication. There is a parallel increase in the cerebral concentration of the barbiturate when epinephrine is added to barbital, but an augmentation of the blood-brain barrier permeability does not completely account for the increase in toxicity.

Mazel & Bush G65,299/69: In mice, epinephrine increases the anesthetic effect and brain concentration of barbital. "The epinephrine effect, however, cannot be attributed to increased brain barbital levels alone, because at 10 min the controls showed no signs of depression with the same brain barbital levels as the 'anesthetized' epinephrine-treated animals."

Hexobarbital ← Epinephrine, Mouse: Reinhard B283/45; Holck B42,745/48*; Holtz et al. C76,300/58*; Mathies et al. D84,334/61**

*Pentobarbital ← Epinephrine + Thyroid extract, Mouse: Ellinwood et al. E39,187/64**

RABBIT

Westfall B31,306/46: In rabbits, pentobarbital sleeping time is shortened by epinephrine and insulin despite their opposite effect upon blood sugar.

Fenu C17,650/54: In rabbits just awakening from thiopental anesthesia, epinephrine i.v. reinduces sleep. A smaller dose of epinephrine injected intracysternally, though equivalent as regards its stressor effects, does not reinduce sleep under these conditions. Since other stressors likewise failed to share this effect of epinephrine, the latter cannot be merely due to an activation of the pituitary-adrenocortical axis.

Cahn et al. G71,537/56: In rabbits, the prolongation of barbiturate (Kemithal, Mebúbarbital) anesthesia by 5-HT is further prolonged by phentolamine, neostigmine and several other drugs, whereas epinephrine and pantheline have an opposite effect.

Savoldi et al. C92,984/60: In rabbits, epinephrine, unlike norepinephrine, causes rapid awakening from thiopental anesthesia.

RAT

Milošević C39,053/56: In rats, epinephrine i.p. administered almost simultaneously with thialbarbital i.v. prolongs anesthesia. The effect of several other anesthetics (chloral hydrate, paraldehyde, tribromoethanol, chlorobutanol, chloralose and ethanol) is likewise significantly prolonged by epinephrine pretreatment. Norepinephrine, cobefrine, synephrine, suprifen and ephedrine also prolong thialbarbital anesthesia, whereas amphetamine and methamphetamine exert an inverse effect. The somewhat contradictory earlier literature on the effect of catecholamines upon anesthesia is briefly reviewed.

Slocombe C14,144/56: In rats under thiopental anesthesia, epinephrine, norepinephrine, adrenochrome, and 5-HT cause a flattening of the electrical activity both at cortical and at subcortical sites.

MAN

von Reis C76,244/59: In patients with barbiturate intoxication, norepinephrine i.v. is beneficial presumably because it prevents anuria by inhibiting the hypotension.

Hexobarbital ← Epinephrine: Fouts D43,347/62, G76,304/63

Hexobarbital ← Norepinephrine + Phenoxybenzamine: Dixon et al. G11,757/64

Benzol ←

Dautrebande 8,083/32: In dogs, benzol inhalation during epinephrine treatment tends to produce fatal collapse.

Caffeine ←

Johnson & Siebert C91,021/28; C91,037/28: In rabbits, the cardiac lesions produced by caffeine are greatly aggravated by concurrent treatment with epinephrine.

Carbon Tetrachloride ←

Hermann et al. 10,215/31; Hermann & Vial 32,885/35: In dogs, fatal ventricular

fibrillation is elicited by epinephrine not only when the hormone is given in combination with chloroform but also when administered with CCl_4 or CH_2Cl_2 .

Furukawa F71,711/65: In rats, hepatic steatosis produced by CCl_4 is inhibited by adrenalectomy and, to some extent, also by hypophysectomy. Corticoids restore the effect of CCl_4 after adrenalectomy; epinephrine does not but it increases the effect of corticoids. STH does not counteract the effect of hypophysectomy. Alloxan diabetes inhibits CCl_4 -induced hepatic lipidosis.

Larson & Plaa F29,496/65: In rats, infusion of large amounts of epinephrine or norepinephrine did not potentiate the hepatotoxic effect of CCl_4 nor did it induce CCl_4 -like hepatic lesions after transection of the spinal cord. These and other observations suggest that protection of the liver against CCl_4 -induced lesions by cervical cordotomy is not due to blockade of adrenergic mechanisms but to reduced hepatic metabolism consequent to hypothermia.

Rice et al. G55,767/67: In isolated perfused rat livers, the hemodynamic effects of norepinephrine are increased by CCl_4 .

Schwetz & Plaa G67,000/69: In mice, the hepatotoxicity of CCl_4 i.p. is greatly increased by simultaneous treatment with epinephrine or norepinephrine s.c. "Epinephrine and norepinephrine may play a secondary potentiating role in CCl_4 -induced hepatotoxicity."

Strubelt et al. G80,282/70: In rats, norepinephrine did not augment the hepatotoxicity of CCl_4 or allyl alcohol at doses of 0.25 mg/kg or less. However, at the dose of 1 mg/kg, at which norepinephrine itself causes liver damage, it potentiates the hepatotoxicity of these agents. Earlier claims that CCl_4 causes liver damage only through the massive liberation of endogenous catecholamines could not be confirmed.

Chloral Hydrate ←

Fastier et al. C37,038/57: In mice, chloral hydrate sleeping time is increased by epinephrine, norepinephrine, phenylephrine, methoxamine, 5-HT, histamine, ergotamine, yohimbine and atropine. "It is suggested that some, at least, of the drugs which prolong the effects of hypnotics do so by virtue of a hypothermic action." Vasopressin, cortisone and DOC did not prolong chloral hydrate sleeping time at the doses tested.

Chloroform ←

Davis & Whipple 58,731/19: In dogs, pretreatment with epinephrine protects against the production of hepatic necrosis produced by chloroform anesthesia. This resistance requires several days of pretreatment and cannot be obtained by a single epinephrine injection just before chloroform administration.

Bardier & Stillmunkès 25,803/26: The collapse produced by epinephrine + chloroform is inhibited by scorpion and vipera venom [species is not stated but presumably dog (H.S.).] In dogs, epinephrine injected during chloroform anesthesia readily produces collapse and death. Injected before chloroform, epinephrine is harmless at similar dose levels. Indeed, pretreatment with epinephrine can protect the dog against subsequent combined administration of chloroform plus epinephrine.

Hermann et al. 10,215/31; *Hermann & Vial* 32,885/35: In dogs, fatal ventricular fibrillation is elicited by epinephrine not only when the hormone is given in combination with chloroform but also when administered with CCl_4 or CH_2Cl_2 .

Tournade & Raymond-Hamet 7,426/32: In dogs, norepinephrine i.v. produces fatal collapse during chloroform anesthesia.

Velluda & Russu 38,782/36: In dogs, chloroform-epinephrine collapse can be prevented by lithium carmine.

Szilágyi et al. D21,498/61: In dogs, the epinephrine-chloroform syncope is inhibited by hypothermia.

Chlorpromazine ← Epinephrine:
Fouts D43,347/62, G76,304/63

Cholesterol ← cf. also Selye G60,083/70, pp. 358, 359.

Trentini et al. G71,152/68: In rabbits, the cholesterol-atherosclerosis-inhibiting effect of Tween 80 is diminished both by 5-HT and by norepinephrine.

Hamprecht G69,560/69: Review (7 pp., 153 refs.) on the mechanisms regulating cholesterol synthesis. A special section deals with the effect of thyroid hormones, steroids, epinephrine, norepinephrine and glucagon.

Cocaine ←

Avant & Weatherby C81,325/60: Review on the inhibition of the systemic toxicity of various local anesthetics by admixture of epinephrine which delays their absorption. Personal observations on mice showed that among five cocaine derivatives, only one

(tetracaine) exhibited considerably decreased systemic toxicity upon addition of epinephrine to the s.c. injected anesthetic.

Curare ←

Bremer & Titeca 23,673/28: In decerebrate cats, the abolition of rigidity by curare is counteracted by epinephrine i.v.

Maddock et al. B18,670/48: In dogs, intraarterial injection of epinephrine blocks the effect of i.v.-administered curare upon the musculature. This blockade is abolished by Dibenamine.

Constantin & Bouyard H15,750/69: In rabbits, the muscular paralysis produced by alcuronium is inhibited by epinephrine presumably through an α -adrenergic mechanism.

Cyclohexylamine ← cf. Selye G60,083/70, pp. 358, 363.

Digitalis ←

Ghedini & Ollino A21,128/14: Brief mention of observations on rabbits showing that epinephrine i.v. "favorably influences" the hemodynamic actions of digitalin, whereas pancreatic powder influences them "unfavorably."

Lage & Spratt F86,237/67: In mice, norepinephrine does not influence the toxicity of digitoxigenin. However, the protection by reserpine against digitoxigenin poisoning is inhibited by large doses of norepinephrine which "would suggest that the depletion of catecholamines by reserpine may be responsible for the protection."

Morrow G47,272/67: In dogs under pentobarbital anesthesia, ouabain tolerance was diminished by large doses of norepinephrine. "The studies suggest that a therapeutic level of digitalis may become toxic during the administration of large doses of norepinephrine."

Ergotamine ←

Tinel & Ungar 14,897/33: In guinea pigs, epileptoid convulsions are produced by epinephrine given conjointly with ergotamine, peptone or yohimbine.

Ethanol ←

Hiestand et al. B78,576/53: In mice, alloxan diabetes and epinephrine increase, whereas insulin decreases, sensitivity to lethal doses of ethanol.

Ethanol ← Epinephrine, Mouse:
Hiestand et al. B78,576/53*

Formalin ←

Gasic B17,561/47: In mice, pretreatment with epinephrine increased resistance to this catecholamine but not to formalin. Apparently, at least under these conditions, cross-resistance does not occur.

Ganglioplegics ←

Page & Taylor B24,841/47: In earlier publications, epinephrine "has been recommended as the antidote of choice after excessive doses of tetraethyl ammonium chloride." In the present experiments on dogs, it is shown that under certain circumstances, especially during pentobarbital anesthesia, TEA may considerably sensitize to the pressor effect of epinephrine, renin and angiotensin.

Byrne C46,341/56: In rabbits, the effect of various drugs upon pulmonary embolisms produced by graphite particles has been investigated. "The combination of epinephrine and tetraethyl-ammonium was dangerous, since epinephrine is a ganglion blocking agent and enhances the effect of tetraethyl-ammonium."

Orione C37,851/56: Guinea pigs are protected by epinephrine against the hypothermia and mortality of hexamethonium intoxication.

Halothane ←

Nikki & Rosenberg G71,574/69: In mice, shivering and hypothermia are prevented by norepinephrine and 5-HT but not by dopamine. "The results suggest that brain catecholamines participate in the control of shivering and return of normothermia after halothane anesthesia in mice."

Hexamethonium ← cf. Ganglioplegics

Lathyrogens ← cf. also Selye G60,083/70, pp. 358, 361.

Kohn & Rivera-Velez F73,678/65: In rats made lathyric by APN fumarate, the vasoconstrictor effect of norepinephrine is diminished.

Lead Acetate ← cf. Selye C19,425/65, p. 137.

Meperidine ←

Radouco-Thomas et al. E60,201/57: In guinea pigs, the analgesic effect of meperidine is diminished by reserpine and counteracted by concurrent administration of norepinephrine.

Meprobamate ←

Belaval & Widen C76,528/58: In a few patients, some of the effects of meprobamate intoxication were antagonized by norepinephrine.

Mescaline ←

Speck C31,193/57: In rats, epinephrine inhibits the bradycardia and hypoglycemia but not the mortality induced by mescaline.

Schopp et al. E92,442/61: In the dog, epinephrine (like KCl and neostigmine) can oppose the paralyzing action of mescaline.

Methanol ←

Severin & Bashkurov G49,801/67: In patients with acute methanol poisoning, combined treatment with norepinephrine, cortisone and various other agents facilitated recovery. [In view of the complex treatment given, it is impossible to ascertain the relative value of each component of the therapeutic regimen (H.S.).]

Methoxyflurane ←

Catton G71,124/69: In rabbits given epinephrine i.v., methoxyflurane anesthesia depends largely upon CO₂ and O₂ tensions.

Methyltropolone ←

Murnaghan & Mazurkiewicz D68,260/63: In mice, the toxicity of 4-methyltropolone is greatly increased by epinephrine. "The results suggest that the in vivo effects of methyltropolone are not only due to inhibition of O-methyltransferase but are also due to a blockade at both alpha and beta receptor sites. Blockade of alpha receptors by methyltropolone suggests that attachment of the ring hydroxyls of the adrenergic amine is a prerequisite for excitation at this receptor."

Morphine ←

Miller et al. G73,877/55: Review of earlier literature suggesting that morphine analgesia is mediated through the release of epinephrine from the adrenal medulla. It had been claimed that adrenalectomy decreases the pain reaction threshold to morphine and that morphine itself has an analgesic effect. However, in the authors' experiments on rats these observations could not be confirmed and TEA failed to reverse the effect of morphine on pain. In mice,

near lethal doses of epinephrine or norepinephrine were required to raise the pain threshold.

Heller et al. H2,707/68: In mice, epinephrine, norepinephrine, and isoproterenol possess a certain analgesic effect of their own and enhance analgesia produced by morphine.

Heller et al. H13,896/68: In mice and rats, the analgesic effect of morphine is increased by epinephrine or norepinephrine i.v.

Nicotine ←

Hueper 91,722/43: In rats, the cardiovascular lesions produced by chronic nicotine intoxication are aggravated both by epinephrine and by DOC.

Papain ← cf. also *Selye C50,810/58, p. 106; C92,918/61, p. 110; G60,083/70, pp. 358, 361.*

Zacco & Pratesi B37,559/47: In guinea pigs, papain shock can be prevented by pre-treatment with epinephrine.

Paraoxon ←

de Candole C25,237/56: In rabbits, resistance to the anticholinesterase paraoxon is increased, under certain conditions, by norepinephrine.

Paraphenylenediamine ←

Meissner E52,567/19: The head and neck edema produced by paraphenylenediamine in the rabbit is not prevented by epinephrine, posterior pituitary extract or thyroid extract.

Tainter 25,429/26; 23,737/28: In rabbits, the head and neck edema produced by paraphenylenediamine is inhibited by epinephrine and related catecholamines.

Cohen et al. 92,880/33: In rabbits, paraphenylenediamine-induced head and neck edema is delayed but not completely abolished by epinephrine.

Pentylenetetrazol ←

Schmidt & Matthies D34,219/62: In mice, 5-HT or norepinephrine injected into certain regions of the brain is without effect upon pentylenetetrazol injections in itself, but counteracts the inhibitory effect of intracerebrally injected reserpine.

Schmidt E32,188/63: In mice, pentylenetetrazol convulsions are inhibited by combined administration of 5-HT and norepinephrine into certain regions of the brain.

Kobrin & Seifter F74,422/66: In one day old chicks, in which the blood-brain barrier is

still incompletely formed, various ω -amino acids as well as 5-HT, histamine and epinephrine, produce sleep and prevent pentylenetetrazol convulsions.

Jones & Roberts G60,654/68: In mice, the convulsive effect of pentylenetetrazol is inhibited by norepinephrine administered intra-cerebroventricularly.

Schlesinger et al. G69,565/69: In mice, intracranial injections of 5-HT or norepinephrine protect against pentylenetetrazol convulsions.

Peptone ←

Hanzlink & Karsner 10,286/20: In guinea pigs, epinephrine can prevent true anaphylactic shock but not the anaphylactoid shock produced by peptone, dextrin or agar. The arsphenamine-induced disturbances (which have been regarded by some as anaphylactoid) are diminished by epinephrine, presumably as a consequence of its circulatory action.

Tinel & Ungar 14,897/33: In guinea pigs, epileptoid convulsions are produced by epinephrine given conjointly with ergotamine, peptone or yohimbine.

Pesticides ←

Cueto Jr. G72,544/70: In dogs, o,p'-DDD produces a selective glucocorticoid deficiency due to its damaging effect upon the fasciculata and reticularis of the adrenal. Epinephrine and norepinephrine produce hypotensive failure in DDD-treated dogs presumably as the consequence of their stressor action. Prednisolone largely restores the resistance of the DDD-treated animals.

Phenylethylamine ←

Fischer et al. G48,517/67: In mice pretreated with iproniazid (as a MAO-inhibitor), phenylethylamine produces amphetamine-like motor effects which are inhibited by epinephrine.

Picrotoxin ←

Saito et al. E27,616/63: In mice, picrotoxin convulsions are inhibited by the intracerebral administration of epinephrine or 5-HT.

Picrotoxin ← Epinephrine: Holck D28,543/49*

Plasmocid ← cf. *Selye C50,810/58, p. 110; C92,918/61, p. 83; C92,918/61, pp. 96, 110; G60,083/70, pp. 358, 361.*

Potassium ←

Lum H22,940/70: In anesthetized dogs, epinephrine i.v. protected against the lethal effects of potassium i.v.

Procaine ←

Cole & Hulpius B32,910/49; B57,578/50: In dogs the toxicity of procaine is not consistently counteracted by epinephrine.

Reserpine ←

Schmidt & Matthies D34,219/62: In mice, 5-HT or norepinephrine injected into certain regions of the brain is without effect upon pentylenetetrazol injections in itself, but counteracts the inhibitory effect of intracerebrally injected reserpine.

Agostini & Giagheddu G14,490/63: Reserpine catalepsy in guinea pigs is inhibited by various folliculoid, testoid and corticoid hormones as well as by epinephrine.

Simionovici et al. F43,099/65: In mice, epinephrine and norepinephrine, as well as histamine, offer partial protection against reserpine intoxication (sedation blepharoptosis, hypothermia). 5-HT has no such effect.

Sparteine ←

Christian D1,675/11; Christian et al. C81,653/11: In rabbits given concurrent treatment with sparteine and epinephrine, cardiac and hepatic lesions develop which are not seen if either of these agents is given alone.

Strychnine ←

Falta & Jvcovic A1,273/09: In frogs and guinea pigs, epinephrine protects against strychnine-induced convulsions, even if the two compounds are injected in different points of the body.

Januschke 50,228/10: In frogs, epinephrine i.v. does not protect against strychnine intoxication. Protection following treatment with mixtures of the two compounds by routes other than i.v. is ascribed to a delay in strychnine absorption.

Bálint & Molnár 34,586/11: In guinea pigs, the fatal effect of strychnine intoxication is inhibited by epinephrine or thyroid extract i.p.

Marañón & Aznar 46,926/15: In frogs, the fatal convulsions produced by strychnine can be prevented if, prior to injection, the drug is

mixed with extracts of the posterior pituitary, the thyroid, various other tissues, and particularly epinephrine. [The possibility of delayed absorption owing to local vasoconstriction has not been considered (H.S.).]

Amici C5,836/54: In mice, mortality from acute strychnine intoxication can be diminished by epinephrine and norepinephrine as well as by some of their derivatives.

**Tetraethylammonium (TEA) ← cf.
Ganglioplegics****Tremorine ←**

Falutz F85,463/67: In cats, tremorine-induced tremor is uninfluenced by norepinephrine and epinephrine but inhibited by L-dopa.

Tween 80 ←

Scilabra & Pugliese G68,796/68; Trentini et al. G71,152/68: In cholesterol-fed rabbits, norepinephrine inhibits the anti-atheromatous action of Tween 80.

Urethan ←

Pradhan et al. C13,632/56: In 3 strains of mice, urethan sleeping time was greatly increased by epinephrine and norepinephrine. Phenobarbital sleeping time was only mildly increased by epinephrine.

Vitamin D, DHT ← cf. also Selye C92,918/61, pp. 183, 188; G19,425/65, p. 137; G60,083/70, pp. 358, 361.

de Bosányi 367/25: In rats kept on a vitamin-D deficient diet, the healing of rickets can be initiated by epinephrine.

Yohimbine ←

Tinel & Ungar 14,897/33: In guinea pigs, epileptoid convulsions are produced by epinephrine given conjointly with ergotamine, peptone or yohimbine.

Varia ←

Schou E92,436/61: Review (23 pp., 147 refs.) on factors influencing the absorption of drugs from subcutaneous connective tissue. Special sections deal with the effect of epinephrine, folliculoids and glucocorticoids which can alter the actions of various drugs by modifying their absorption rate.

Microorganisms, Vaccines and Venoms ←

Comparatively few investigators dealt with the effect of catecholamines upon bacterial infections. In guinea pigs, infection with *Clostridium welchii* is enhanced by the addition of epinephrine to the inoculum and, in rats, acute hypertension produced by epinephrine (or angiotensin) facilitates the production of pyelonephritis by *E. coli*. Topical resistance to inoculation with various pathogenic microbes is diminished by the injection of epinephrine into the site of inoculation.

Injection of epinephrine conjointly with various viruses enhances their infectivity in mice. In rabbits, herpes simplex infection followed by norepinephrine treatment may cause plaques of demyelination in the central nervous system.

At the beginning of this century, it has been claimed that epinephrine can inactivate bacterial toxins, e.g., diphtheria or tetanus toxin in guinea pigs, mice and rabbits, both *in vivo* and *in vitro*. It has subsequently been shown, however, that neutralization only occurs if epinephrine and the toxin, are mixed before injection, presumably because the vasoconstrictor hormone delays absorption. In rabbits, combined administration of typhoid toxin and norepinephrine produces cardiac necroses. Data on the effectiveness of catecholamines in preventing endotoxin shock in various species are rather conflicting. Under certain circumstances, combined treatment with endotoxin and epinephrine produces a generalized Shwartzman-Sanarelli phenomenon in the rabbit.

In rats, complete blockade of the sympathetic function greatly diminishes resistance to endotoxins and this effect can be counteracted by epinephrine.

In guinea pigs, intoxication with cobra venom applied to skin erosions can be inhibited by the delay of absorption that results from topical treatment with epinephrine.

Bacteria ←

Lauber 9,102/32: Observations on the effect of vasopressin, epinephrine, thyroid extract and insulin upon streptococcal and staphylococcal infections in mice.

Evans et al. B65,652/48: In guinea pigs and rabbits, epinephrine diminishes local resistance to a large series of pathogenic microbes.

Bishop & Marshall C95,338/60: In guinea pigs, infection with *Clostridium welchii* is greatly enhanced by addition of epinephrine in oil or water to the inoculum.

Jones & Shapiro D55,793/63: In rats, an acute episode of hypertension produced by epinephrine or angiotensin i.v. facilitates the production of pyelonephritis following infection with *E. coli*.

Viruses ←

Sellers H10,893/69: In mice, epinephrine or 5-HT injected simultaneously with various viruses i.v. enhances their infectivity and their penetration into the brain.

Connor H23,400/70: In rabbits, infection with herpes simplex followed by treatment with norepinephrine may cause plaques of demyelination in the subcortical white matter and brain-stem. Possibly, in man, disseminated sclerosis is "multifactorial in origin" resulting from an apparently innocuous infection with herpes simplex in childhood followed later by challenge through physical or mental stress resulting in norepinephrine liberation. [A largely speculative "Letter to the Editor" (H.S.).]

Bacterial Toxins ← cf. also *Selye* E5,986/66, pp. 14, 72; G60,083/70, p. 362.

Marie 37,085/13: In guinea pigs, the lethal effect of diphtheria or tetanus toxin s.c. is diminished by previous incubation with epinephrine.

Marie 32,348/18; 37,087/19: In mice and rabbits, tetanus toxin is largely inactivated by epinephrine *in vivo* or *in vitro*.

Tawara 12,478/21: In mice, the lethal effect of tetanus toxin is not significantly influenced by epinephrine unless the two

compounds are mixed before injection. This neutralizing effect may be due to the acidity of the epinephrine solution employed, since various acids are equally effective.

Mezzano & Peluffo D9,328/60: In rabbits, combined administration of typhoid toxin and norepinephrine produces cardiac necrosis not observed following treatment with either of these agents alone.

Altura et al. F43,209/65: In rats, norepinephrine and angiotensin fail to prolong survival after traumatic shock, temporary ligation of the superior mesenteric artery or endotoxin shock. However, vasopressin (PLV-2) was significantly effective in traumatic and intestinal ischemia shock but not in endotoxinemia.

Patel & Rao G36,076/65: In mice, epinephrine offers virtually no protection against tetanus toxin.

Vick F48,509/65: In the dog, cortisol and/or isoproterenol cause temporary improvement in endotoxin shock but no increase in survival time.

Bruce & Brunson F79,682/67: In dogs, mortality from endotoxin shock is diminished after pretreatment with norepinephrine. Survival is further improved by concurrent administration of the tranquilizer propiomazine.

Kutner et al. G46,379/67: In dogs, norepinephrine considerably decreases thoracic-duct lymph-flow both under normal conditions and during endotoxin shock.

Zeller et al. F92,117/67: In rats, simultaneous treatment with endotoxin and large amounts of 5% glucose solution i.v. produces a generalized "Shwartzman reaction" which can be blocked by phenoxybenzamine but is not modified by norepinephrine.

Brown et al. H456/68: In dogs, survival from endotoxin shock was improved by combined treatment with norepinephrine and adrenergic blockade.

Hruza & Stetson Jr. H455/68: Pretreatment with depot epinephrine or norepinephrine increased resistance to trauma in the Noble-Collip drum and to endotoxin.

Anas et al. G64,139/69: In dogs, norepinephrine, isoproterenol and phenoxybenzamine increase oxygen consumption during endotoxin shock. In this respect, norepinephrine is most active, but its effect is transient.

Boler et al. G65,722/69: "Treatment of endotoxin-shocked dogs with propiomazine and levarterenol promoted their survival and prevented or reduced the severity of most of

the previously described ultrastructural alterations of the liver."

Barksdale et al. H21,684/70: In rabbits prepared and challenged for the generalized Shwartzman reaction by two i.v. injections of endotoxin spaced at an interval of 24 hrs, "epinephrine treatment was shown to increase the mortality when the normal optimum dose of endotoxin was used, ie, 100 µg per injection, but did not increase the incidence of the generalized Shwartzman reaction. When sublethal doses of endotoxin were used, ie, 25 µg or 10 µg, epinephrine treatment profoundly increased the mortality and incidence of the generalized reaction."

Krawczak & Brodie H25,296/70: In rats, complete blockade of sympathetic function can be achieved by demedullation combined with reserpine-like agents (depleting catecholamine stores), bretylium-like agents (preventing nerve impulse from releasing catecholamines) or ganglioplegics. Following such total sympathetic blockade, mortality from histamine or endotoxin is as markedly increased as by adrenalectomy. Pretreatment with epinephrine alone counteracts the increased lethality of endotoxin and histamine after sympathetic blockade. Cortisone pretreatment only partially corrects the sensitization by adrenalectomy, whereas cortisone + epinephrine offers complete protection against these agents. Presumably, sympathetic stimulation is "the first line of defense against the vasoconstrictor disturbance elicited by endotoxin and histamine." The lethal effect of formalin or tourniquet shock is likewise greatly increased by adrenalectomy but, in contrast to that of endotoxin and histamine, it cannot be increased by sympathetic blockade. Furthermore, cortisone alone counteracts the toxicity of these stressors in adrenalectomized rats. Apparently "formalin and tourniquet shock is initiated by a mechanism which differs from that elicited by histamine and endotoxin and does not primarily involve the sympathetic system."

Venoms ←

Bardier & Stillmunkes 13,522/23: In dogs and rabbits, scorpion venom exerts cardiovascular actions similar to those of epinephrine but does not produce collapse during chloroform anesthesia. The pharmacologic interactions between the venom and epinephrine are briefly discussed.

Douglas 21,321/24: In guinea pigs, intoxication with cobra venom applied to skin erosions can be inhibited by the delay of absorption that results from topical treatment with epinephrine.

Stahnke F 57,253/65: In rats treated with various scorpion and snake venoms, resistance was decreased by pretreatment with heat, cold or epinephrine. In all three cases, the change in resistance is ascribed to stress as such.

Immune Reactions ←

In guinea pigs and dogs, anaphylactic shock can be inhibited by epinephrine and norepinephrine. In rats, allegedly large amounts of epinephrine depress antibody formation against sheep serum. In rabbits, massive doses of epinephrine + norepinephrine decrease the incidence of chicken anti-rabbit-kidney nephritis.

Hanzlik & Karsner 10,286/20: In guinea pigs, epinephrine can prevent true anaphylactic shock but not the anaphylactoid shock produced by peptone, dextrin or agar. The arsphenamine-induced disturbances (which have been regarded by some as anaphylactoid) are diminished by epinephrine, presumably as a consequence of its circulatory action.

Marmorston-Gottesman & Perla 23,446/28: In rats, large amounts of epinephrine, injected repeatedly before and after injection of an

antigen (sheep serum), depress antibody formation.

Cirstea & Suhaciu G 2,471/63: In dogs, anaphylactic shock is diminished by epinephrine and norepinephrine.

Hinton et al. G 21,390/64: In rabbits, large doses of epinephrine + norepinephrine decrease the incidence of chicken anti-rabbit-kidney nephritis. Fluorescent antibody studies "suggest the final antigen-antibody reaction may be of lesser magnitude in the treated animals."

Ionizing Rays ←

In mice, cutaneous purpura produced by heavy X-irradiation is allegedly inhibited by adrenochrome. Resistance to total body X-irradiation is increased by numerous amines including norepinephrine, epinephrine, histamine and 5-HT, allegedly because these compounds reduce the oxygen tension in tissues. Even topical treatment with norepinephrine is said to protect the hair follicles against radiation injury.

In rats, mortality after total body X-irradiation is likewise diminished by epinephrine; similar observations with epinephrine and its derivatives have been made in guinea pigs, hamsters and chicks.

Hervé & Lecomte B 46,855/49: In mice, the cutaneous purpura produced by heavy X-irradiation is inhibited by adrenochrome semicarbazone.

Gray et al. B 68,316/52: In rats, pretreatment with either epinephrine or vasopressin diminishes mortality after total body X-irradiation.

Gray et al. B 69,100/52: In rats, pretreatment with Pitressin or epinephrine increases survival following exposure to lethal X-irradiation.

Bacq D 77,006/54: In mice, resistance to whole body X-irradiation is increased by numerous amines, particularly cysteamine

(β -mercaptoethylamine), norepinephrine, 5-HT and histamine.

Stearner et al. B 92,163/54: In chicks, both epinephrine and decreased oxygen tension protect against mortality from X-irradiation. Presumably both agents act by decreasing oxygen supply to tissues during an early phase of the events initiated by ionizing rays.

Rigat C 10,747/55: Review (46 pp., 67 refs.) on the literature concerning the effect of hormones upon X-irradiation with special reference to ACTH, STH, vasopressin, epinephrine, cortisone, DOC, testosterone, estradiol, progesterone, and thyroxine.

van der Meer & van Bekkum G71,673/59: In mice, the radioprotective effect of histamine, epinephrine and other biologic amines is related to their pharmacologic activity and can be blocked by their pharmacologic antagonists. "It is concluded that histamine, epinephrine and a number of other biological amines protect against irradiation by reducing the oxygen tension in the spleen and possibly in other blood forming organs."

Semenov D7,087/60: In mice, 5-HT offers better protection against radiation sickness than epinephrine although the latter is also

effective, especially when given in combination with acetylcholine.

Gabler G40,828/66: In guinea pigs and rats, mortality from whole body X-irradiation is diminished by epinephrine and metaproterenol.

Letov H19,253/68: In mice, topical treatment with norepinephrine protects the hair follicles against radiation-induced injury.

Prewitt & Musacchia H16,155/69: In hamsters exposed to ^{60}Co radiation, survival was improved by pretreatment with norepinephrine > epinephrine and > isoproterenol. It is dubious whether these agents act simply through tissue hypoxia.

Cold ←

In rats, in which gastrointestinal ulcers were produced as part of an alarm reaction elicited by cold or other stressors, epinephrine p.o. produces lung edema, presumably because the hormone is well absorbed from the wound surfaces of the stress ulcers. Also in rats, epinephrine "appears to improve survival during exposure to cold, and adaptation to low temperatures increases the calorogenic effect of norepinephrine." However, depending upon circumstances, the catecholamines may also have an adverse effect upon survival during exposure to cold. In cold adapted guinea pigs, nonshivering thermogenesis is induced by cold or norepinephrine. It is suggested that nonshivering thermogenesis is essentially a catecholamine-mediated mechanism.

In dogs, norepinephrine infusions during cooling reduce the incidence of ventricular fibrillation, whereas epinephrine has an opposite effect.

In minipigs, nonshivering thermogenesis plays a major role in adaptation to cold only during neonatal life, if at all. Epinephrine and norepinephrine fail to stimulate nonshivering thermogenesis in minipigs, whereas they do have this effect in cold adapted rats.

In the ground squirrel, norepinephrine produces nonshivering thermogenesis after curarization.

De Gaetani 33,111/35: In dogs, the cardiovascular changes produced by epinephrine are greatly altered by exposure to cold.

Selye A8,052/38: Rats and guinea pigs normally tolerate very large doses of epinephrine or histamine p.o. but these substances cause toxic manifestations (lung edema, emphysema) if administered following the production of an alarm reaction by cold, forced muscular exercise or other stressors. Presumably the gastrointestinal lesions characteristic of the alarm reaction facilitate the absorption of substances which normally do not traverse the intestinal epithelium in active form.

DesMarais & Dugal B51,093/50; B64,359/51: In rats exposed to cold, epinephrine

"appears to improve survival." [Brief abstract without details (H.S.).]

Hannon & Larson D4,112/61: In rats, the effect of norepinephrine upon calorogenesis and the mobilization of nonesterified fatty acids is considerably modified by cold.

Evonuk & Hannon E21,027/63: In rats, adaptation to cold increases the calorogenic effect of norepinephrine.

Schönbaum et al. E21,028/63: In rats, norepinephrine (like epinephrine) has an adverse effect upon survival during exposure to cold. This effect is less pronounced following adaptation to cold. Adrenal-demedullated animals (whether receiving guanethidine or not) showed evidence of acclimation to cold. "These observations suggest that increased

amounts of adrenaline and noradrenaline in tissues or circulation are not essential for acclimation."

Leblanc & Pouliot F4,622/64: In rats, norepinephrine facilitates adaptation to cold.

Pohl & Hart F62,568/66: In the ground squirrel (*Citellus tridecemlineatus*), exposure to cold or injection of norepinephrine produced nonshivering thermogenesis after curarization.

Zeisberger & Brück F89,184/67; Zeisberger et al. F89,185/67: In cold-adapted guinea pigs, nonshivering thermogenesis is induced by exposure to cold or by injection of norepinephrine. Several observations suggest "that the nonshivering thermogenesis in the guinea pig

is essentially due to a catecholamine-mediated mechanism."

Angelakos & Daniels G64,739/69: In dogs, infusion of norepinephrine during cooling reduced the incidence of ventricular fibrillation, whereas epinephrine had an opposite effect.

Brück et al. H13,180/69: In minipigs, as in most species other than the rat, nonshivering thermogenesis plays a major role in adaptation to cold only during neonatal life if at all. Epinephrine and norepinephrine, which stimulate considerable nonshivering thermogenesis in cold-adapted adult rats, failed to do so in minipigs.

Other Stressors ←

In rats, various adrenergic blocking agents inhibit, whereas epinephrine increases mortality during traumatic shock in the Noble-Collip drum. However, some investigators failed to observe any effect of epinephrine or norepinephrine upon this type of shock; indeed, occasionally they noted an increase in resistance when the catecholamines were administered in the form of depots.

In rabbits, survival following trauma in the Noble-Collip drum has been said to be moderately improved by epinephrine and other vasopressor amines. On the other hand, rabbits, made tolerant to normally lethal doses of epinephrine, showed an increased susceptibility to "rotational shock," whereas drum-tolerant animals were less susceptible to the lethal effect of epinephrine.

Death from hypoxia in rats kept in closed vessels is accelerated by epinephrine. Mortality from hyperoxygenation (exposure to 6 atmospheres of oxygen) is increased in rats by pretreatment with epinephrine, whereas survival from hemorrhagic shock is improved by long-lasting infusions of norepinephrine.

Small doses of epinephrine or norepinephrine prolong the duration of electrically-induced seizures in the rat.

In rats, irreversible hypovolemic shock, produced by complete occlusion of the portal vein, is effectively combated by continuous infusions of norepinephrine, whereas epinephrine has an inverse effect.

In rats, with complete blockade of the sympathetic nervous system, epinephrine considerably increases resistance to certain stressors (endotoxin, histamine) but not to others (formalin, tourniquet shock). Apparently, the adrenergic system is of special importance only in combating certain types of stress.

Trauma ←

Levy et al. C10,848/54: In rats, various adrenergic-blocking agents increase resistance to traumatic shock (Noble-Collip drum), whereas epinephrine has an opposite effect.

Noble C10,541/55: In rats, mortality from trauma in the Noble-Collip drum is strikingly increased by pretreatment with epinephrine

but not diminished by various adrenergic-blocking agents.

Brunson et al. C78,005/59: In rabbits, survival following trauma in the Noble-Collip drum is moderately improved by epinephrine and other vasopressor amines.

Walden & Brunson G5,968/63: Studies on rabbits gradually adapted to trauma in the Noble-Collip drum led to the conclusion that

"animals tolerant to normally lethal doses of epinephrine showed an increased susceptibility to rotational shock, but drum tolerant animals were less susceptible to lethal doses of epinephrine."

Altura et al. F 36,124/65; F 43,209/65: In rats, survival following temporary ligation of the superior mesenteric artery was improved by PLV-2 but not by epinephrine or angiotensin. The associated changes in the microcirculation of the meso-appendix are described.

Cronin & Tan F 29,408/65: In dogs, the inotropic effect of norepinephrine is increased during cardiogenic shock elicited by closed-chest coronary embolization.

Hruza & Stetson Jr. H 455/68: In rats, pretreatment with depot epinephrine or norepinephrine increased resistance to trauma in the Noble-Collip drum and to endotoxin.

Calof & Smith H 10,412/69: In rats, mortality from traumatic shock (Noble-Collip drum) is not modified by epinephrine or norepinephrine but considerably reduced by various β -adrenergic agents.

Hruza & Zweifach G 77,195/70: Rats adapted to trauma in a Noble-Collip drum show an increased catecholamine content in their fat tissue and an increased resistance to epinephrine. Conversely, rats rendered resistant to epinephrine or norepinephrine become more resistant to trauma in the Noble-Collip drum. [This may be one of the mechanisms involved in the induction of cross resistance (H.S.).]

Hypoxia and Hyperoxygenation ←

Campbell A 14,903/37: In rats exposed to six atmospheres of oxygen in a pressure chamber, subsequent decompression is better tolerated at low than at high external temperatures. "Using an external temperature of 24°C and white rats of about 80 g, the following substances, administered subcutaneously, are found to enhance oxygen poisoning: thyroxin (0.4 mg), dinitrophenol (1.5 mg), ac-tetrahydro- β -naphthylamine (0.5 c.c., 1 p.c.), adrenalin (0.02 mg), pituitary extract (posterior lobe, above 3.5 units), insulin (0.025 u.) and eserine (0.045 mg administered with atropine 0.075 mg). These doses in themselves are harmless."

Keminger G 42,501/66: In rats, death from lack of oxygen in closed vessels is accelerated by T3 and retarded after thyroidectomy or cortisone treatment. Epinephrine further accelerates mortality in hyperthyroid animals.

Hemorrhage ←

Lansing et al. C 30,227/57: In rats, survival from hemorrhagic shock is improved by long-lasting infusions of norepinephrine.

Electric Stimuli ←

Minz & Domino B 81,852/53: In rats, small doses of epinephrine or norepinephrine prolong the duration of electrically-induced seizures. Since glucose, ACTH and cortisone failed to prolong seizure duration, it is unlikely that epinephrine acts by release of these substances. Histamine depressed the cortical response to electroshock.

Varia ← cf. also *Selye* B 40,000/50, p. 64; B 58,650/51, p. 53; G 60,083/70, pp. 358, 361.

Mejia et al. G 60,637/68: In rats with irreversible hypovolemic shock produced by complete occlusion of the portal vein, neither cortisol pretreatment nor adrenalectomy influenced the survival time, whereas selective extirpation of the adrenal medulla or continuous infusion of norepinephrine increased it. Similar infusion of epinephrine decreased survival time.

Krawczak & Brodie H 25,296/70: In rats, complete blockade of sympathetic function can be achieved by demedullation combined with reserpine-like agents (depleting catecholamine stores), bretylium-like agents (preventing nerve impulse from releasing catecholamines) or ganglioplegics. Following such total sympathetic blockade, mortality from histamine or endotoxin is markedly increased as by adrenalectomy. Pretreatment with epinephrine alone counteracts the increased lethality of endotoxin and histamine after sympathetic blockade. Cortisone pretreatment only partially corrects the sensitization by adrenalectomy, whereas cortisol + epinephrine offers complete protection against these agents. Presumably, sympathetic stimulation is "the first line of defense against the vasomotor disturbance elicited by endotoxin and histamine." The lethal effect of formalin or tourniquet shock is likewise greatly increased by adrenalectomy but, in contrast to that of endotoxin and histamine, it cannot be increased by sympathetic blockade. Furthermore, cortisol alone counteracts the toxicity of these stressors in adrenalectomized rats. Apparently "formalin and tourniquet shock is initiated by a mechanism which differs from that elicited by histamine and endotoxin and does not primarily involve the sympathetic system."

Hepatic Enzymes ←

For the effect of adrenergic agents upon hepatic enzyme induction *cf.* the Abstract Section as well as the individual toxicants, whose metabolism is affected (*cf.* "Drugs").

Dixon et al. G11,757/64: In the rat, both norepinephrine and adrenergic blocking agents inhibit the hepatic drug-metabolizing enzyme activity as judged by tests *in vitro*.

Terayama & Takata F69,475/66: Epinephrine markedly reduces the N-demethylating activity of rat liver.

← SPECIAL SURGICAL PROCEDURES***← Thymectomy***

Hormones and Hormone-Like Substances ←. During the early part of this century, a great deal of work has been done on the influence of thymus extract upon the toxicity of thyroid preparations. In tadpoles, thyroid extract inhibits growth, and concurrent administration of thymus extract neutralizes this effect. In mice, the toxic manifestations of thyroid feeding are allegedly inhibited also by feeding thymus tissue.

In pigeons, the loss of weight elicited by thyroid extract or thyroid feeding is inhibited by dietary administration of thymus tissue. This effect could not be duplicated by equivalent amounts of nucleic acid preparations, but the specificity of an antithyroid thymus principle remains in doubt.

In rats, the hypercalcemia and osteitis fibrosa produced by parathyroid extract overdosage are said to be inhibited by concurrent treatment with a thymus extract and thymectomy is claimed to raise histamine resistance, but all these findings require confirmation.

Cameron & Carmichael 27,015/25: In young rats, feeding of desiccated thyroid frequently produces tetany, perhaps as a consequence of the decreased blood supply to the entire thyroparathyroid apparatus. This tetany cannot be influenced by simultaneous feeding of thymus.

Kříženecký & Podhradský 4,186/26: In frog tadpoles, feeding of thyroid extract inhibits growth; concurrent administration of thymus extract neutralizes this effect.

Sklower 25,299/27: In mice, the toxic manifestations of thyroid feeding can be inhibited by concurrent thymus feeding. Earlier literature on antagonistic interactions between thyroid and thymus is reviewed.

Kříženecký 4,176/28; 23,688/28; 277/30: In pigeons, the loss of weight produced by desiccated thyroid is greatly diminished by concurrent administration of a thymus extract. Equivalent amounts of nucleic acid preparations do not have this effect. "The thymus appears to be a regulator of the thyroid gland."

Scholtz 4,272/32: In rats, the hypercalcemia and osteofibrosis produced by excess parathyroid extract are inhibited by concurrent treatment with thymus extract.

Weltman & Sackler D14,302/61: In adult rats, thymectomy raises resistance to histamine and to swimming in cold water. The effect is ascribed to a raised resistance to nonspecific stress. [The results are not statistically significant (H.S.).]

Drugs ←. The thymus involution of the alarm reaction is one of the most sensitive indicators of exposure to the stress of any toxicant, yet, we have very little evidence to show that the thymus could influence resistance to drugs. Except for the well-known immunologic disturbances produced by neonatal thymectomy, neither

removal of the organ nor treatment with extracts of its tissue succeeded in altering general resistance in a significant and reproducible manner.

It has been stated that the hepatic changes caused in rats by such carcinogens as dimethylaminoazobenzol are diminished by treatment with thymus extract, and that in newborn mice, the induction of pulmonary tumors by DMBA is facilitated by the injection of neonatal thymus tissue. Furthermore, in neonatal mice, the otherwise permanent immunosuppression induced by DMBA can be reversed by syngenic thymus, bone marrow, or spleen cell transplants.

Probably, one of the first observations on the effects of neonatal thymectomy was that removal of the thymus during the first days of life increases the sensitivity of the rabbit to morphine, heroin, and codeine. However, the change in resistance was not very pronounced and was presumably due to the general debilitation of neonatally thymectomized animals.

At about the same time, it had been claimed that thymus extract decreases the sensitivity to thallium intoxication in mice, but this observation has never been confirmed.

Resistance to vitamin A or vitamin D is not significantly affected in rats thymectomized at 2-3 weeks of age. The claim that thymectomy partially protects the adult rabbit against overdosage with irradiated ergosterol remained unconfirmed. In vitamin-D deficient rats, the development of rickets could not be significantly altered by lipid soluble thymus extracts.

Anaphylactoidogens ← cf. Selye G 46,715/
68, pp. 180, 184, 200.

Carcinogens ←

Fumarola & Giordano D 33,779/62: In rats, the production of tumors by benzpyrene is allegedly somewhat inhibited after thymectomy and accelerated by treatment with thymus extract.

Potop et al. E 39,894/62: In rats, the hepatic changes produced by dimethylaminoazobenzol are diminished by treatment with a thymus extract.

Simpson et al. F 2,965/64: In rats, neonatal thymectomy did not significantly influence the induction of tumors by DMBA.

Balner & Dersjant G 37,980/66: In mice, neonatal thymectomy does not significantly influence the induction of cutaneous tumors by intradermal 3-MC administration. Surprisingly, tumor incidence in mice with depressed homograft reactivity was, if anything, lower than in the immunologically competent animals.

Grant et al. F 66,117/66: In mice, the induction of cutaneous papillomas and carcinomas by 3,4-benzopyrene is accelerated by neonatal thymectomy. "It may be that some tumours initiated by benzopyrene do not differ sufficiently from the host to evoke a homograft

reaction against them even when the immunological competence is unimpaired. It may be that factors such as the growth-rate of the tumour allow it to progress in spite of a reaction against it, or it may be that under some conditions an animal may become specifically tolerant to a tumour which it bears."

Allison & Taylor F 83,300/67: From experiments on mice treated with DMBA and various viruses, "it is concluded that neonatal thymectomy does not consistently increase the incidence of chemically induced tumors but does increase the incidence of tumors after exposure to polyoma and SV40 viruses and adenovirus type 12."

Flaks F 95,414/67: In mice, the induction of pulmonary tumors by DMBA, soon after birth, is intensified by injections of neonatal thymus tissue.

Smieciński & Górska H 20,765/68: In 2-3 week old female mice, topical tumorigenesis by intravaginal application of 20-methylcholanthrene is "slightly retarded" by thymectomy. This effect has been tentatively ascribed to the removal of "promine," an allegedly tumor growth-stimulating substance of thymic origin. [The results do not lend themselves to statistical evaluation (H.S.).]

Ball & Dawson G 67,723/69: In neonatal mice "the permanent immunosuppression

induced by DMBA could be reversed by the injection of normal syngeneic bone marrow and spleen cells but not with thymic implants."

Kobayashi H27,113/69; H27,114/69: In mice, thymectomy inhibits the production of cutaneous papillomas by DMBA, whereas transfusion of thymus cells has an opposite effect.

Schneiberg & Gorski G68,745/69: In mice, thymectomy followed by whole-body X-irradiation increases the incidence of skin cancers after serial spraying with methylcholanthrene. In itself, neither thymectomy nor X-irradiation was effective in this respect.

Cholesterol ← cf. Selye G60,083/70, p. 442.

Chloroform ←

Bomskov et al. A 56,954/42: In rats and guinea pigs, sensitivity to chloroform can be diminished by a thymus extract.

Curare ←

Blaw et al. F65,571/66: In mice, neonatal thymectomy increases the sensitivity of the myoneural junction to blockade by tubocurarine.

Morphine ←

Arima 60,156/35: In rabbits thymectomized during the first few days of life, sensitivity to morphine, heroin, and codeine is slightly diminished. Treatment with thymus extract has an opposite effect.

Sulfa Drugs ← cf. Selye G60,083/70, p. 442.

Thallium Acetate ←

Buschke et al. 43,284/33; 4,823/33: In mice, thyroxine increases, whereas thymus extract decreases sensitivity to intoxication with thallium acetate.

Vitamin A ←

Vogt et al. B36,750/48: In rats thymectomized at 2–3 weeks of age, resistance to vitamin-A or vitamin-D deficiency was not significantly affected.

Vitamin C ←

Lopez-Lomba 17,165/23: In guinea pigs, thymectomy prolonged survival on a vitamin-C deficient diet. [The difference was not impressive (H.S.).]

Vitamin D ←

Coppo 3642/32: In rabbits, thymectomy does not characteristically influence the syndrome of overdosage with irradiated ergosterol.

Messini & Coppo 31,827/35: In rabbits, thymectomy partially protects against intoxication with irradiated ergosterol.

Vogt et al. B36,750/48: In rats thymectomized at 2–3 weeks of age, resistance to vitamin-A or vitamin-D deficiency was not significantly affected.

Nassi G1,107/62; G1,108/62: In vitamin-D deficient rats, treatment with a lipid soluble thymus extract did not significantly affect the development of rickets.

Microorganisms, Parasites and Their Products ←. Despite several claims to the contrary, there does not seem to be any convincing evidence that thymectomy or thymus extracts have any specific effect upon bacterial infections.

Mice thymectomized at birth become extremely resistant to the virus of lymphocytic choriomeningitis, but this infection may aggravate the course of the wasting syndrome produced by neonatal thymectomy. The susceptibility of neonatally thymectomized mice against this virus is restored by implants of Millipore diffusion chambers containing newborn thymic tissue. It is assumed that the neurologic symptoms in mice and man result from an antigen-antibody reaction in the brain which can be prevented by neonatal thymectomy.

In newborn mice infected with polyoma virus, neonatal thymectomy delays mortality of certain strains only. Inoculation of polyoma virus into neonatally thymectomized weanling hamsters resulted in tumor formation, whereas sham operated litter mates developed no neoplasms. Apparently, "neonatal thymectomy may render some resistant animals susceptible to the effects of an oncogenic virus."

In inbred BALB/c mice, inoculated with **Rauscher virus**, thymectomy did not influence the erythroblastic reaction, but thymectomy did alter the response to a variety of other viruses in various species.

In neonatally thymectomized mice, susceptibility to infection with **C. albicans** is increased.

In chickens from embryos inoculated in ovo with testosterone, after about one week of incubation, the bursa of Fabricius spleen and thymus are permanently atrophic and the antibody formation against repeated infection with **Eimeria tenella** fails to develop antibodies. Surgical thymectomy 90 min after hatching was rarely complete and did not constantly block immunization against **Eimeria tenella**.

Neonatally thymectomized rats infected with **P. berghei** are highly subject to parasitemia, whereas neonatally thymectomized hamsters are comparatively resistant and develop the disease slowly. It is postulated that the thymectomized hamsters failed to develop an antibody that normally causes microembolization of the cerebral capillaries with agglutinated parasites.

In neonatally thymectomized mice, susceptibility to the toxic effects of **E. coli** or **S. typhosa** endotoxins is increased.

Bacteria and Vaccines ←

Cody & Code G4,417/63: In rats sensitized with *Bordetella pertussis* vaccine, the anaphylaxis produced by challenge with horse serum is inhibited by concurrent thymectomy and splenectomy but not by thymectomy alone.

Schäfer B99,955/54: Monograph (127 pp., numerous refs.) on the role of endocrine factors in tuberculosis. Special sections are devoted to the hormones of the thyroid, parathyroid, thymus, adrenals, pancreas, and gonads.

Kratter & Martelli B60,263/49: In adult rabbits, thymectomy increases susceptibility to staphylococcus infection.

Viruses ←

Lymphocytic Choriomeningitis ←. *Levey et al. E30,471/63:* In mice, neonatal thymectomy protects against the virus of lymphocytic choriomeningitis, but susceptibility is restored by implants of Millipore diffusion chambers containing newborn thymic tissue. "A humoral mechanism of action of the tissue in the chamber is proposed."

Rowe et al. E29,673/63; East et al. E38,279/64; Földes et al. G29,263/65: Mice thymectomized at birth become resistant to lymphocytic choriomeningitis virus infection.

Szeri et al. G56,565/66: In mice, infection with lymphocytic choriomeningitis virus accelerates and aggravates the course of the wasting syndrome produced by neonatal thymectomy.

Schmuñis et al. G55,003/67: In mice, neonatal thymectomy protects against lymphocytic choriomeningitis produced by Junin virus. Presumably, the "neurological symptoms in mice and human patients result from an antigen-antibody reaction in the brain and that this reaction between the virus and its antibody is prevented by thymectomy."

Polyoma ←. *Kodama & Moore D56,877/63:* In newborn mice infected with polyoma virus, thymectomy (performed two weeks later) delayed mortality in the AKR but not in the C3H strain. The incidence and latency of parotid tumors were not affected by thymectomy in either strain.

Lang G55,002/68: "Inoculation of polyoma virus into weanling hamsters, thymectomized as neonates, has resulted in the production of tumors. In contrast, the sham operated litter mates developed no demonstrable neoplasms over a 12–18 month period of observation. Thus, it has been confirmed in these studies that neonatal thymectomy may render some resistant animals susceptible to the effects of an oncogenic virus."

Rauscher ←. *Dunn & Green G40,311/66:* In inbred BALB/c mice inoculated with Rauscher virus "thymectomy had no apparent effect on the erythroblastic reaction, while splenectomy intensified the process in the liver and erythroblastic foci appeared in the lymph nodes. Granulocytopenia was also stimulated in some mice."

Varia ←. *Dunn E 29,253/63*: "When BALB/c mice given the Moloney virus were thymectomized, splenectomized or subjected to both procedures, the incidence of lymphocytic leukemia was reduced." *Li et al. E 33,523/63*: Various types of calf thymus extracts exhibit antiviral and antibacterial activity *in vitro*.

Crispens & Rey F 87,332/67: In mice, neonatal thymectomy increases sensitivity to lactate dehydrogenase virus.

van Hoosier Jr. et al. F 78,860/67: In hamsters, thymectomy facilitates tumor formation by weakly oncogenic adenoviruses.

Jahkola et al. G 47,813/67: In mice, the infection by cytomegalic inclusion virus is aggravated by thymectomy.

Yohn et al. G 57,790/68: In hamsters given adenovirus-12, strain Huie, s.c. at birth, thymectomy at one week of age increased tumor incidence in both sexes, although it remained higher in females as is usually the case. Cortisone treatment, begun at one week of age, increased tumor incidence but, again, this remained higher in females. Antibody responses to adenovirus-12 T-antigen were depressed in thymectomized and cortisone-treated animals.

Fungi and Yeasts, Parasites ←

Candida Albicans ←. *Salvin et al. G 30,533/65; F 35,876/65*: In mice thymectomy diminishes resistance to infection with *C. albicans* as well as to the endotoxins of *E. coli* and *S. typhosa* but not to *C. albicans* endotoxin.

Eimeria ←. *Pierce & Long G 36,006/65*: Chickens from embryos inoculated in ovo with testosterone hatched between the 6th and 9th day of incubation without a detectable bursa of Fabricius; their spleen and thymus weights were also significantly reduced. These fowls failed to develop antibodies as a result of repeat-

ed infection with *Eimeria tenella*. Surgical thymectomy 90 min after hatching was rarely complete and did not consistently lead to a failure of immunization against *E. tenella*.

Rose & Long G 74,020/70: Review of the literature with personal observations on the effect of thymectomy and removal of the bursa of Fabricius upon *Eimeria* infections in the chicken.

Plasmodium Berghei ←. *Stechschulte H 15,256/69*: "Neonatally thymectomized rats infected with *P. berghei* develop higher percentage parasitemias and have a higher percentage mortality than sham-operated animals."

Brown et al. H 1,304/68: In rats, neonatal thymectomy decreases resistance to infection with *P. berghei*. [Although throughout the paper the authors speak of rats, in their conclusion they refer to mice (H.S.).]

Wright H 1,836/68: In hamsters, neonatal thymectomy delays death from infection with *P. berghei*. "It is postulated that the non-thymectomized animals develop an agglutinin, in response to the malarial infection, that causes microembolisation of the cerebral capillaries with agglutinated parasitised RBC, and that neonatal thymectomy inhibits or delays the production of this agglutinin."

Trypanosoma Lewisi ←. *Perla & Marmorston-Gottesman 810/30*: In young rats, thymectomy diminishes, whereas orchidectomy increases the severity of *T. lewisi* infection.

Bacterial Toxins ←

Salvin et al. G 30,533/65; F 35,876/65: In mice, thymectomy diminishes resistance to infection with *C. albicans* as well as to the endotoxins of *E. coli* and *S. typhosa*, but not to *C. albicans* endotoxin.

Immune Reactions ←. The extensive literature on neonatal thymectomy upon immune reactions is beyond the scope of this monograph and should be consulted in the reviews cited in the Abstract Section which are specifically devoted to this topic. Let us point out merely that in rats sensitized with *Bordetella pertussis* vaccine, anaphylaxis to horse serum is inhibited by concurrent thymectomy and splenectomy, but not by thymectomy alone. In adult rats which had been neonatally thymectomized, the production of nephrotoxic serum nephritis remains possible.

Kemény et al. B 66,729/51: In guinea pigs, both ovariectomy and orchidectomy diminish anaphylactic shock, whereas thymectomy has no effect upon it.

Miller E 37,260/63: Review on the role of the thymus in immunity.

Cody & Code G 4,417/63: In rats sensitized with *B. pertussis* vaccine, the anaphylaxis

produced by challenge with horse serum is inhibited by concurrent thymectomy and splenectomy, but not by thymectomy alone.

Fisher & Fisher F690/64: In adult rats which had been neonatally thymectomized, the production of nephrotoxic serum nephritis

remains possible. This "indicates that progression of the disease is not necessarily dependent upon those immunologic functions related to thymic function, at least during the time interval studied."

Hepatic Lesions ←. In partially hepatectomized adult rats, thymectomy inhibits mitotic proliferation of the hepatocytes, but does not significantly affect the associated enzymic changes.

Forabosco & Narducci G70,746/69; Forabosco & Toni G70,747/69; Forabosco & Guli G70,748/69; Forabosco et al. G70,749/69: In

adult rats, thymectomy inhibits mitotic proliferation in hepatocytes after partial hepatectomy. Earlier literature is reviewed.

Ionizing Rays ←. In mice, thymectomy increases the incidence of epithelial tumor formation after X-irradiation. Thymus transplants do not significantly influence the incidence of leukemia.

In neonatally thymectomized mice, both thymus implants and cystamine tend to correct the comparatively low X-ray resistance. The intercapillary glomerulosclerosis produced by neonatal X-irradiation is potentiated by neonatal thymectomy, but reduced by splenectomy in mice. In adult, unlike in neonatal mice, thymectomy does not reduce resistance to total body X-irradiation. X-ray resistance is restored in neonatally thymectomized mice by the i.p. implantation of thymus-bearing diffusion chambers.

O'Gara & Ards D12,341/61: In mice, thymectomy appears to increase the incidence of epithelial tumors following X-irradiation. In thymectomized mice bearing intrasplenic thymus transplants, the incidence of leukemia was not significantly altered in comparison to thymectomized controls.

Méwissen & Lagneau G14,713/64: In mice thymectomized at 40 days of age, cystamine retains its protective action, and implantation of a thymus lobe likewise increases resistance.

Goedbloed & Vos G33,427/65: In mice, neonatal thymectomy had little if any effect on the incidence of secondary disease in radiation chimeras.

Méwissen et al. F45,017/65: Mice thymectomized during the first days of life show a very low resistance to total body X-irradiation, but this can be improved by thymus transplants.

Guttman G45,255/67: In mice, the intercapillary glomerulosclerosis produced by neonatal X-irradiation is potentiated by neonatal thymectomy but reduced by splenectomy.

Schneiberg et al. G56,009/67; G58,580/67: In three-week old mice, thymectomy reduces natural resistance to whole body X-irradiation, but this is not the case in rats thymectomized at a later age.

Schneiberg et al. G69,791/68: In mice, sensitization to X-irradiation produced by thymectomy is restored by i.p. implantation of thymus-bearing diffusion chambers, presumably owing to the production of a humoral lymphopoietic factor by the thymus implant.

Schneiberg et al. G58,579/68: In mice, thymectomy does not significantly affect the blood protein changes produced by acute X-irradiation, although it does increase mortality.

Varia ←. In germ-free mice, the lethality of parabiotic intoxication is aggravated by neonatal thymectomy, presumably because here the thymus-dependent immune reactions are actually beneficial. Adaptive enzyme formation does not appear to be significantly affected by neonatal thymectomy in the rat.

Cold ←

Weltman & Sackler D14,302/61: In adult rats, thymectomy raises resistance to histamine and to swimming in cold water. The effect is ascribed to a raised resistance to nonspecific stress. [The results are not statistically significant (H.S.).]

Tumors ←

Potop et al. F 38,309/65: In the mouse and rat as well as in chick embryos, the growth of various experimental tumors is stimulated by a lipoprotein extract of the thymus.

Parabiosis ←

Anderson et al. H 11,186/69: In germ-free mice, the lethality of parabiotic intoxication

is aggravated by neonatal thymectomy. "It is concluded that with respect to parabiotic union of germ-free mice, the primary consequence of neonatal thymectomy is a dampening of the characteristic anemia-polycythemia which is not associated with an enhanced survival, and that thymic dependent immune reactions may actually promote survival."

Hepatic Enzymes ←

Bonetti et al. G 48,030/67: Induction of hepatic TPO-activity by tryptophan i.p. is not prevented by postnatal thymectomy in the rat. These observations do not confirm the view that adaptive enzyme formation depends upon a mechanism similar to that of immunologic defense.

← Splenectomy

Splenectomy does not appear to have any conspicuous effects upon detoxicating mechanisms.

It has been claimed that immunosuppression induced by neonatal administration of **DMBA** in mice could be reversed by syngenic spleen, bone marrow, or thymus cell implants. In rats sensitized with *B. pertussis* vaccine, the anaphylaxis produced by challenge with horse serum is inhibited by concurrent splenectomy and thymectomy, but not by thymectomy alone. In certain inbred strains of mice inoculated with *Rauscher virus*, splenectomy intensified the erythroblastic reaction in the liver, whereas thymectomy had no such effect. In rats, splenectomy does not significantly alter the regeneration of the liver after **partial hepatectomy**, although some investigators claimed that splenectomy accelerates it. This acceleration does not occur if the spleen is reimplanted into either the portal or the systemic circulation. However, all these claims have been challenged by some investigators.

The intercapillary glomerular sclerosis produced by neonatal **X-irradiation** in mice is said to be reduced by splenectomy.

Drugs ←

Ball & Dawson G 67,723/69: In neonatal mice "the permanent immunosuppression induced by **DMBA** could be reversed by the injection of normal syngenic bone marrow and spleen cells but not with thymic implants."

Brodeur & Marchand H 37,030/71: In rats, splenectomy significantly decreases cytochrome P-450 during the first few days after the operation but not at seven days. **Parathion, p-nitroanisole and zoxazolamine** metabolism is also decreased, whereas that of **hexobarbital** is unchanged during the first four days after

splenectomy. Apparently, splenectomy inhibits certain hepatic microsomal enzymes, perhaps by influencing the blood supply of the liver.

Microorganisms and Vaccines ←

Cody & Code G 4,417/63: In rats sensitized with *B. pertussis* vaccine, the anaphylaxis produced by challenge with horse serum is inhibited by concurrent thymectomy and splenectomy, but not by thymectomy alone.

Dunn E 29,253/63: "When BALB/c mice given the *Moloney virus* were thymectomized, splenectomized or subjected to both procedu-

res, the incidence of lymphocytic leukemia was reduced."

Dunn & Green G40,311/66: In inbred BALB/c mice inoculated with Rauscher virus "thymectomy had no apparent effect on the erythroblastic reaction, while splenectomy intensified the process in the liver and erythroblastic foci appeared in the lymph nodes. Granulocytopenia was also stimulated in some mice."

Hepatectomy Partial ←

Pontremoli & Arrigo D63,528/50: In rats partially hepatectomized and splenectomized simultaneously, hepatic regeneration is just as rapid, and sometimes even accelerated, in the absence of the spleen.

Trasino B56,794/50: In rats, splenectomy does not significantly alter the regeneration of the liver remnant after partial hepatectomy.

Zaltzman D92,764/56: Splenectomy enhances regeneration of the liver after partial hepatectomy in the rat.

Pérez-Tamayo & Romero D38,897/58: In rats, splenectomy stimulates hepatic regeneration after partial hepatectomy. This acceleration does not occur if the spleen is reimplanted either into the portal circulation or s.c. Apparently, a humoral factor is involved.

Molimard & Benozio G75,048/70: In rats, splenectomy does not influence hepatic regeneration after partial hepatectomy, but the latter operation causes an increase in splenic weight.

Ionizing Rays ←

Guttman G45,255/67: In mice, the intercapillary glomerulosclerosis produced by neonatal X-irradiation is potentiated by neonatal thymectomy but reduced by splenectomy.

← Other Surgical Interventions

← **Pinealecstasy.** In rats, pinealecstasy inhibits the induction of hepatic cancers by some but not by all carcinogens.

← **Sympathectomy.** The extensive literature on the effect of sympathectomy with or without adrenal demedullation has been discussed in many earlier review articles to which the reader must be referred. Suffice it here to summarize certain recent investigations which show that in rats, complete blockade of the sympathetic function by demedullation combined with reserpine-like, bretylium-like or ganglioplegic agents, increases mortality from histamine or endotoxin as much as does complete adrenalectomy. Pretreatment with epinephrine alone counteracts this diminished resistance. On the other hand, the lethal effect of other stressors such as formalin or tourniquet shock is greatly increased by adrenalectomy, but not by a sympathetic blockade. In this event cortisone is especially effective in restoring resistance. Apparently "formalin and tourniquet shock is initiated by a mechanism which differs from that elicited by histamine and endotoxin and does not primarily involve the sympathetic system."

← Pinealecstasy

Jelinek & Křeček H2,778/68: In young, unlike in adult rats, pinealecstasy inhibits the adrenal regeneration hypertension that results from an excessive mineralocorticoid production by the regenerating adrenal cortex.

Lacassagne et al. G74,931/69: In rats, removal of the pineal inhibits the induction of hepatic cancers by 4-dimethylaminoazobenzene, but does not influence the carcinogenic effect of 2-acetylaminofluorene and diethylnitrosamine.

Aubert & Bohouon G77,483/70: In hamsters, certain carcinogens (DMBA, urethan) induce

melanomas, preceded by depigmentation. Epiphysectomy does not alter this result.

← Sympathectomy

Krawczak & Brodie H25,296/70: In rats, complete blockade of sympathetic function can be achieved by demedullation combined with reserpine-like agents (depleting catecholamine stores), bretylium-like agents (preventing nerve impulse from releasing catecholamines) or ganglioplegics. Following such total sympathetic blockade, mortality from histamine or endotoxin is as markedly increased as by adrenalectomy. Pretreatment with epine-

phrine alone counteracts the increased lethality of endotoxin and histamine after sympathetic blockade. Cortisone pretreatment only partially corrects the sensitization by adrenalectomy, whereas cortisone + epinephrine offers complete protection against these agents. Presumably, sympathetic stimulation is "the first line of defense against the vaso-motor disturbance elicited by endotoxin and histamine." The lethal effect of formalin or

tourniquet shock is likewise greatly increased by adrenalectomy but, in contrast to that of endotoxin and histamine, it cannot be increased by sympathetic blockade. Furthermore, cortisone alone counteracts the toxicity of these stressors in adrenalectomized rats. Apparently "formalin and tourniquet shock is initiated by a mechanism which differs from that elicited by histamine and endotoxin and does not primarily involve the sympathetic system."

← HISTAMINE

Drugs ←. Histamine does not considerably influence drug-resistance in general, but it does tend to increase the anesthetic effect of barbiturates, chloral hydrate and several other hypnotics.

In rats given lead acetate i.v., subcutaneous injection of histamine causes topical calcergy, and if the dose of histamine is large, this may be associated with widespread calcification in the autonomic nervous system ("neurocalcergy").

Varia ←. Sensitivity to histamine is greatly increased in mice by pretreatment with B. pertussis vaccine, but resistance to botulinum toxin and nereis toxin is not affected.

Several investigators reported that histamine offers protection against total body X-irradiation in mice. It has also been claimed that histamine aggravates the pulmonary lesions produced by hyperoxygenation and depresses the cortical response to electroshock. On the other hand, an alarm reaction produced by exposure to cold increases the toxicity of orally administered histamine in rats, presumably because the amine is readily absorbed from the exulcerated gastrointestinal mucosa.

Drugs ←

Acetonitrile ←. Wuth A 48,026/21: In mice, tyramine and diiodotyramine—like thyroid extract—offer protection against acetonitrile, histamine does not.

Barbiturates ←. Werle & Lentzen A 28,007/38: In dogs and rabbits, various vasoactive substances (epinephrine, histamine, vasopressin, kallikrein) tend to prolong the anesthetic effect of pronarcon and hexobarbital.

Fastier D 95,950/56: In mice, 5-HT considerably potentiates the hypnotic effect of cyclobarbital and chloral hydrate. However, this property is not very specific, since bufotenine, tryptamine, histamine, and epinephrine likewise prolong cyclobarbital hypnosis. Literature on numerous other drugs which prolong barbiturate anesthesia is cited. "It therefore seems possible that the ability of 5-HT to prolong hypnosis may be due to a relatively unspecific, vascular effect."

Hexobarbital ← Histamine, Mouse: Ambrus et al. C16,607/52*; Bousquet et al. F35,073/65*

Chloral Hydrate ←. Fastier et al. C 37,038/57:

In mice, chloral hydrate sleeping time is increased by epinephrine, norepinephrine, phenylephrine, methoxamine, 5-HT, histamine, ergotamine, yohimbine, and atropine. "It is suggested that some, at least, of the drugs which prolong the effects of hypnotics do so by virtue of a hypothermic action." Vasopressin, cortisone, and DOC did not prolong chloral hydrate sleeping time at the doses tested.

Lead ←. Selye et al. G 11,123/64: "In rats simultaneously given an intravenous injection of lead acetate and a subcutaneous injection of histamine, extensive calcium deposition occurs in various parts of the autonomic nervous system. This neurotropic form of mastocalcergy can be inhibited by pretreatment with various mast-cell dischargers (compound 48/80, polymyxin, chlorpromazine), mast-cell components (histamine, 5-HT) or drugs known to inhibit the pharmacologic actions of such mast-cell components (cyproheptadine, neo-antergan). This prophylactic effect appears to be largely specific to compounds related to mast-cell

activity since it was not shared by various other drugs and stressors tested."

Pentylenetetrazol ←. *Kobrin & Seifter F74,422/66*: In one day old chicks, in which the blood-brain barrier is still incompletely formed, various ω -amino acids as well as 5-HT, histamine, and epinephrine, produce sleep and prevent pentylenetetrazol convulsions.

Reserpine ←. *Simionovici et al. F43,099/65*: In mice, epinephrine and norepinephrine, as well as histamine, offer partial protection against reserpine intoxication (sedation blepharoptosis, hypothermia). 5-HT has no such effect.

Varia ←

Microorganisms, Vaccines, and Bacterial Toxins ←. *Kind E67,787/58*: Review (9 pp., 80 refs.) on increased sensitivity to 5-HT, histamine, and anaphylaxis induced in mice by *B. pertussis* vaccine.

Fishel et al. E8,474/64: Review (8 pp., 26 refs.) on the mechanism of sensitization by *B. pertussis* vaccine to histamine and 5-HT. The published data "indicate that the basis of this hypersensitivity is a blockade of a part of adrenergic division of the sympathetic nervous system. Preliminary experiments are also described, which suggest that a similar mechanism may also be operative in the local Shwartzman reaction."

Simpson H5,300/68: In mice, 5-HT increases, whereas pargyline decreases resistance to both *botulinum toxin* and *nereis toxin*. Histamine has no effect on either intoxication.

Ionizing Rays ←. *Bacq D77,006/54*: In mice, resistance to whole body X-irradiation is increased by numerous amines, particularly cysteamine (β -mercaptoethylamine), norepinephrine, 5-HT, and histamine.

van der Meer & van Bekkum G71,673/59: In mice, the radioprotective effect of histamine, epinephrine, and other biologic amines is related to their pharmacologic activity and can be blocked by their pharmacologic antagonists. "It is concluded that histamine, epinephrine

and a number of other biological amines protect against irradiation by reducing the oxygen tension in the spleen and possibly in other blood forming organs."

Langendorff et al. G34,793/65: In mice, incorporation of ^{59}Fe in the erythrocytes can be used as a test for the radioprotective effect of 5-HT, histamine, and other chemicals.

Langendorff et al. G38,385/65: In mice, an open skin wound considerably increases mortality following total body X-irradiation. After this combined treatment, 5-HT has no protective effect, whereas histamine diminishes mortality.

Langendorff & Messerschmidt G45,424/66: In mice, the effect of 5-HT and histamine upon whole body irradiation combined with standard skin wounds is examined.

Koch G51,862/67: Theoretical considerations on the protective effect of 5-HT and histamine against X-irradiation.

Hyperoxygenation ←. *Grognot & Senelar C41,294/57*: In rats and guinea pigs, the pulmonary inflammation induced by inhalation of pure oxygen at barometric pressure is aggravated by ACTH or histamine.

Electric Stimuli ←. *Minz & Domino B81,852/53*: In rats, small doses of epinephrine or norepinephrine prolong the duration of electrically-induced seizures. Since glucose, ACTH, and cortisone failed to prolong seizure duration, it is unlikely that epinephrine should act by release of these substances. Histamine depressed the cortical response to electroshock.

Cold ←. *Selye A8,052/38*: Rats and guinea pigs normally tolerate very large doses of epinephrine or histamine p.o., but these substances cause toxic manifestations (lung edema, emphysema) if administered following the production of an alarm reaction by cold, forced muscular exercise, or other stressors. Presumably the gastrointestinal lesions characteristic of the alarm reaction facilitate the absorption of substances which normally do not traverse the intestinal epithelium in active form.

← 5-HT

Nonsteroidal Hormones and Hormone-Like Substances ←. Comparatively little is known about the protective effect of 5-HT against overdosage with hormones and related compounds. The duration of hydroxydione anesthesia is prolonged by 5-HT in rats and mice. The toxicity of epinephrine is allegedly unaffected by 5-HT in the mouse, but it is diminished in the rabbit.

Drugs ←. 5-HT greatly potentiates the action of various barbiturates in the mouse, rabbit, and rat.

5-HT is also said to augment the antitumor actions of various chemical carcinogens diminishing at the same time their damaging effect upon the hemopoietic system.

The toxicity of carbon tetrachloride upon rat liver is decreased by 5-HT.

5-HT also prolongs chloral hydrate, ethanol, ether, halothane and chloroform anesthesia and tends to protect rabbits and dogs against curare.

The toxic effects of harmine in chickens are inhibited by 5-HT, whereas the bone lesions caused by lathyrogens in rats are aggravated.

In mice, the depression of spontaneous activity produced by LSD is converted into stimulation by 5-HT, but the prolonging effect of this amine upon hexobarbital narcosis is augmented by LSD.

5-HT potentiates the effects of mephenesin and meprobamate in the mouse. In rabbits, it increases the analgesic effect of morphine.

In rats, 5-HT increases the effects of nitrogen mustard but diminishes the myotoxic action of paraphenylenediamine.

Pentylenetetrazol convulsions are inhibited by combined treatment with 5-HT and norepinephrine in the mouse. 5-HT also antagonizes pentylenetetrazol in newly hatched chicks in which the blood-brain barrier is still incomplete; here the amine has an anesthetic effect. In mice, intracranial injection of 5-HT protects against pentylenetetrazol convulsions. In strains susceptible to audiogenic and pentylenetetrazol-induced seizures, 5-HTP presumably protects because it raises the 5-HT concentration in the brain.

Picrotoxin convulsions are also inhibited by intracerebral administration of 5-HT in mice. On the other hand, the inhibition of pentylenetetrazol convulsions by intracerebrally injected reserpine is counteracted by 5-HT injected into certain regions of the brain.

In dogs, 5-HT inhibits the epilepsy provoked by direct application of strychnine or of an electric current to the brain.

In DHT-sensitized rats, calcification of the submaxillary glands can be obtained by 5-HT given s.c.

Microorganisms and Their Products ←. 5-HT (like histamine) is especially toxic to mice sensitized with Bordetella pertussis vaccine. If injected simultaneously with various viruses i.v., 5-HT tends to enhance their infectivity and their penetration into the brain.

In mice, resistance to botulinum toxin is increased by 5-HT given 30-60 min earlier. 5-HT also increases resistance to various endotoxins in the mouse. This effect, which is greater in females than in males, is potentiated by cortisol and aggravated by thyroxine.

Ionizing Rays ←. In mice, resistance to total body X-irradiation is increased by numerous amines including 5-HT, histamine, norepinephrine, and cystamine. 5-HTP offers similar protection, and the beneficial effect of 5-HT can be enhanced by concurrent administration of other radioprotective substances such as MAO-inhibitors and sulfhydryl-containing compounds. The radioprotective effect of 5-HT has also been confirmed in rats.

Various Stressors ←. 5-HT also increases the resistance of mice against hyper-oxygenation. In rats it is said to decrease resistance to cold. In dogs it inhibits the epilepsy produced by direct electric stimulation of the brain, and in rats it elevates

the EST. The characteristic response of rats treated with methionine sulfoximine is reduced by 5-HT. Finally, in susceptible strains of mice, audiogenic seizures are prevented by 5-HTP, presumably because of the resulting increase in brain 5-HT.

Steroids ← cf. also Selye G60,083/70, p.429.

Bianchi & de Maio C54,169/58: In rats, anesthesia produced by hydroxydione i.p. is aggravated by 5-HT, reserpine or hexamethonium.

Vacek D10,919/61: In mice, 5-HT prolongs the duration of hydroxydione anesthesia, whereas LSD shortens it.

Estradiol ← 5-HT: Inscoe et al. F70,325/66

Nonsteroidal Hormones and Hormone-Like Substances ←

Milošević C41,594/57: In mice, reserpine potentiates the toxicity of epinephrine, but this effect should not be ascribed to depletion of 5-HT, since the latter given i.v. does not significantly modify the lethal effect of epinephrine.

Sanyal G55,044/68: In rabbits, 5-HT prevents production of pulmonary edema by epinephrine.

5-HT(N-acetyl) ← 5-HT: Inscoe et al. F70,325/66

Drugs ←

N-Acetyl-p-aminophenol ← 5-HT: Inscoe et al. F70,325/66

N-Acetyltyramine ← 5-HT: Inscoe et al. F70,325/66

Anaphylactoid Edema ← cf. Selye G46,715/68, p. 201.

Barbiturates ←.

MAN

Poloni D95,333/55; D99,472/55: Studies on the effect of 5-HT upon barbiturate or LSD intoxication in man (especially in schizophrenics) and in leeches.

MOUSE

Shore et al. C18,383/55: In mice, 5-HT markedly potentiates the hypnotic action of hexobarbital. In addition, 5-HT i.v. given to mice which have just recovered from hexobarbital hypnosis, immediately causes them to fall asleep again. Thus, it acts like chlorpromazine or reserpine by increasing the sensitivity of the brain to barbiturates, rather

than like SKF 525-A which inhibits drug detoxication.

Fastier D95,950/56: In mice, 5-HT considerably potentiates the hypnotic effect of cyclobarbital and chloral hydrate. However, this property is not very specific, since bufotinine, tryptamine, histamine, and epinephrine likewise prolong cyclobarbital hypnosis. Literature on numerous other drugs which prolong barbiturate anesthesia is cited. "It therefore seems possible that the ability of 5-HT to prolong hypnosis may be due to a relatively unspecific, vascular effect."

Zanowiak & Rodman C85,018/59: In mice, 5-HT potentiates the effects of various barbiturates, mephenesin, and meprobamate. This potentiation is counteracted by LSD.

Kato C78,047/59: In mice, the prolongation of pentobarbital or hexobarbital sleeping time by 5-HT (administered in the form of its precursor 5-HTP which penetrates the brain barrier more readily) is inhibited by DOPA; the latter presumably acts as a precursor of norepinephrine.

Rümke G76,693/62: In the mouse, hexobarbital anesthesia is prolonged by an immediately preceding i.p. or s.c. injection of 5-HT.

Hexobarbital ← 5-HT, Mouse: Shore et al. C18,383/55*; Sturtevant D87,568/56*; Brown C31,328/57*; Holtz et al. C76,300/58*; Matthies et al. D84,334/61*; Rümke G76,693/62*, G69,768/63*

RABBIT

Antona C11,379/55: In rabbits, large doses of 5-HT increase the duration and depth of thiopental anesthesia.

Cahn et al. G71,537/56: In rabbits, the prolongation of barbiturate (Kemithal, Mebutobarbital) anesthesia by 5-HT is further prolonged by phentolamine, neostigmine, and several other drugs, whereas epinephrine, and pantheline have an opposite effect.

Mantegazzini C33,637/56: In rabbits, the potentiation of pentobarbital anesthesia by 5-HT does not depend upon the hypotensive action of large doses of the latter.

Cahn et al. C64,625/58: In rabbits, thiopental anesthesia is prolonged by pretreatment with 5-HT i.v. This is associated with charac-

teristic changes in the carbohydrate metabolism of the brain.

Lauria & Sharma F67,259/66: In mice, pentobarbital sleeping time is prolonged by 5-HT and several other indole derivatives.

Kadzielawa & Widy-Tyszkiewicz H18,469/69: In mice, p-chlorophenylalanine decreases the duration of hexobarbital sleeping time. This effect is counteracted by 5-HTP, presumably as a consequence of increased 5-HT formation.

RAT

Correll et al. E57,669/52: In rats, anesthesia with various barbiturates or ether diminishes resistance to the lethal effect of 5-HT.

Pierre & Cahn C24,570/55: In rats, 5-HT prolongs thiopental anesthesia, but has no definite effect upon pentobarbital, urethan, or ether narcosis. In rabbits, 5-HT prolongs pentobarbital anesthesia, but has no definite effect upon thiopental and urethan narcosis.

Cahn et al. C19,722/56: In rats thiopental anesthesia is prolonged by 5-HT and this effect can be inhibited by a variety of 5-HT antagonists; further prolongation of sleep is obtained in decreasing order by chlorpromazine, Hydergine, acetylcholine, neostigmine, and phenotolamine.

Slocombe C14,144/56: In rats under thiopental anesthesia, epinephrine, norepinephrine, adrenochrome, and 5-HT cause a flattening of the electrical activity both at cortical and at subcortical sites.

Gaddum C25,117/56: Brief review on the synergism between barbiturates and 5-HT.

Garattini & Valzelli G71,229/56: In rats, the prolongation of pentobarbital anesthesia by 5-HT is influenced by numerous drugs.

Salmoiraghi et al. C21,596/56: 5-HT prolongs the hypnotic action of hexobarbital both in mice and in rats.

Fornaroli C47,728/57: In rats, 5-HT prolongs anesthesia produced by various barbiturates or ether. Earlier literature is reviewed.

Bose et al. D58,773/63: In rats, hexobarbital sleeping time is prolonged by 5-HT. This prolongation is inhibited by Cannabis resin.

Phenobarbital ← 5-HT(N-acetyl): Inscoe et al. F70,325/66

*Bemegride ← 5-HT, Mouse: Rümke G76,692/62**

Carcinolytic Agent ←. Man'ko F74,715/66; F82,459/66: In mice and rats, 5-HT increases the carcinolytic action of dopan, chlorambucil and cyclophosphamide upon certain transplantable tumors, and simultaneously decreases

their damaging effect upon the hemopoietic system.

Carbon Tetrachloride ←. Fiore-Donati et al. C62,200/58; C78,953/59: In rats, 5-HT offers partial protection against the hepatic lesions produced by CCl_4 .

Erspamer E5,915/66: A monograph on 5-HT and related indolealkylamines, with a special section on their protective effect against radiation injury, hepatic cirrhosis produced by CCl_4 or allyl alcohol, and cardiovascular calcifications produced by DHT.

Cholesterol ←. Trentini et al. G71,152/68: In rabbits, the cholesterol-atherosclerosis-inhibiting effect of Tween 80 is diminished both by 5-HT and by norepinephrine.

Chloral Hydrate ←. Fastier D95,950/56: In mice, 5-HT considerably potentiates the hypnotic effect of cyclobarbital and chloral hydrate. However, this property is not very specific, since bufotenine, tryptamine, histamine and epinephrine likewise prolong cyclobarbital hypnosis. Literature on numerous other drugs which prolong barbiturate anesthesia is cited. "It therefore seems possible that the ability of 5-HT to prolong hypnosis may be due to a relatively unspecific, vascular effect."

Fastier et al. C37,038/57: In mice, chloral hydrate sleeping time is increased by epinephrine, norepinephrine, phenylephrine, methoxamine, 5-HT, histamine, ergotamine, yohimbine, and atropine. "It is suggested that some, at least, of the drugs which prolong the effects of hypnotics do so by virtue of a hypothermic action." Vasopressin, cortisone, and DOC did not prolong chloral hydrate sleeping time at the doses tested.

Chloroform ←. Wulfsohn & Politzer D22,421/61: In mice, 5-HT greatly prolongs chloroform anesthesia but has little or no effect upon ether or halothane narcosis.

Curare ←. Sala & Perris C78,420/58: In rabbits treated with D-tubocurarine, 5-HT causes a rapid but transient restoration of neuromuscular transmission.

Schopp & Rife E24,636/63: In dogs, 5-HT exerts a mild antcurare action upon the indirectly stimulated peroneal-tibialis-anticus nerve-muscle preparation.

Ethanol ←. Rosenfeld G72,151/60: In mice, ethanol anesthesia is prolonged by 5-HT, tryptamine, and dopamine. "Analytical data provided experimental proof that the potentiating effect of the aromatic amines was not attributable either to an increase in the brain alcohol content or to an interference with the over-all rate of alcohol destruction in the body."

Ethanol ← 5-HT + Iproniazid,
Mouse: Besendorf et al. C31,623/56*

Ether ←. Fornaroli C47,728/57: In rats, 5-HT prolongs anesthesia produced by various barbiturates or ether. Earlier literature is reviewed.

Wulfsöhn & Politzer D22,421/61: In mice, 5-HT greatly prolongs chloroform anesthesia, but has little or no effect upon ether or halothane narcosis.

Halothane ←. Wulfsöhn & Politzer D22,421/61: In mice, 5-HT greatly prolongs chloroform anesthesia, but has little or no effect upon ether or halothane narcosis.

Nikki & Rosenberg G71,574/69: In mice, shivering and hypothermia are prevented by norepinephrine and 5-HT, but not by dopamine. "The results suggest that brain catecholamines participate in the control of shivering and return of normothermia after halothane anaesthesia in mice."

Harmine ←. Bowman & Osuide F98,712/68: In chickens, the toxic effects of tremorine and harmine are inhibited by 5-HT and numerous other drugs.

Lathyrogens ←. Franchimont et al. D13,136/61: In rats, osteolathyrism produced by AAN is aggravated by 5-HT, whereas glucagon does not modify it significantly.

Lead ←. Selye et al. G11,123/64: "In rats simultaneously given an intravenous injection of lead acetate and a subcutaneous injection of histamine, extensive calcium deposition occurs in various parts of the autonomic nervous system. This neurotropic form of mastocalcergy can be inhibited by pretreatment with various mast-cell dischargers (compound 48/80, polymyxin, chlorpromazine), mast-cell components (histamine, 5-HT) or drugs known to inhibit the pharmacologic actions of such mast-cell components (cyproheptadine, neo-antergan). This prophylactic effect appears to be largely specific to compounds related to mast-cell activity since it was not shared by various other drugs and stressors tested."

LSD ←. Poloni D95,333/55; D99,472/55: Studies on the effect of 5-HT upon barbiturate or LSD intoxication in man (especially in schizophrenics) and in leeches.

Brown C31,328/57: In mice, the depression of spontaneous activity induced by LSD is converted into stimulation by 5-HT.

Salmoiraghi & Page C38,518/57: In mice, LSD and various other hallucinogens (bufotenine, mescaline, ibogaine) augment the pro-

longing effect of 5-HT upon hexobarbital narcosis.

Mephenesin, Meprobamate ←. Zanowiak & Rodman C85,018/59: In mice, 5-HT potentiates the effects of various barbiturates, mephenesin, and meprobamate. This potentiation is counteracted by LSD.

Mercury ←. Erspamer B84,587/53: In rats given large doses of HgCl₂ survival is prolonged and mortality decreased by repeated s.c. injections of 5-HT, perhaps because the latter diminishes renal blood flow.

Methionine Sulfoximine ←. Wada et al. G48,380/67: Rats treated with methionine sulfoximine show a characteristic response to audiogenic stimuli, which is reduced by 5-HT and increased by DOPA.

Morphine ←. Nicák F47,918/65: In rats and mice, the analgesic effect of small doses of morphine is potentiated by 5-HT.

Saarnivaara H2,855/68; G71,565/69: In rabbits, 5-HT increases morphine analgesia.

Nitrogen Mustard ←. Uroć et al. E37,637/64: In rats, 5-HT increases the toxicity of mustine hydrochloride (nitrogen mustard), a typical radiomimetic poison.

Ballerini & Bosi G31,956/65: In rats, 5-HT increases the lethality of intoxication with uracil mustard. Antiserotonin have an opposite effect.

Paraphenylenediamine ←. Jasmin & Bois C73,640/59; C83,058/60: In rats, the myotoxic action of paraphenylenediamine can be partially prevented by 5-HT, but also by KCl, methylene blue, and vitamin C. The mechanism of protection is not understood.

Pentylenetetrazol ←. Bonnycastle et al. C37,036/57: In rats, anticonvulsants increase the 5-HT concentration of the brain, but administration of 5-HT, iproniazid, or 5-hydroxytryptophan, in doses which elevate the brain levels of 5-HT, did not protect against the convulsant or lethal action of pentylenetetrazol.

Schmidt & Matthies D34,219/62: In mice, 5-HT or norepinephrine injected into certain regions of the brain is without effect upon pentylenetetrazol injection in itself, but counteracts the inhibitory effect of intracerebrally injected reserpine.

Schmidt E32,188/63: In mice, pentylenetetrazol convulsions are inhibited by combined administration of 5-HT and norepinephrine into certain regions of the brain.

Seifter et al. G71,087/63: In chicks, pentylenetetrazol convulsions can be inhibited by 5-HT and some of its analogues.

Kobrin & Seifter F74,422/66: In one day old chicks, in which the blood-brain barrier is still incompletely formed, various ω -amino acids as well as 5-HT, histamine, and epinephrine, produce sleep and prevent pentylenetetrazol convulsions.

Schlesinger et al. G61,802/68: In susceptible mice, audiogenic and pentylenetetrazol-induced seizures are prevented by 5-HTP, presumably because of the resulting increase in brain 5-HT concentration.

Schlesinger et al. G69,565/69: In mice, intracranial injections of 5-HT or norepinephrine protect against pentylenetetrazol convulsions.

Pentylenetetrazol ← 5-HTP + Genetics, Mouse: Schlesinger et al. G61,802/68*

Picrotoxin ←. *Saito et al. E27,616/63:* In mice, picrotoxin convulsions are inhibited by the intracerebral administration of epinephrine or 5-HT.

Plasmocid ← cf. Selye G60,083/70, p. 429.

Reserpine ←. *Schmidt & Matthies D34,219/62:* In mice, 5-HT or norepinephrine injected into certain regions of the brain is without effect upon pentylenetetrazol injection in itself, but counteracts the inhibitory effect of intracerebrally injected reserpine.

Simionovici et al. F43,099/65: In mice, epinephrine and norepinephrine, as well as histamine, offer partial protection against reserpine intoxication (sedation blepharoptosis, hypothermia). 5-HT has no such effect.

Strychnine ←. *Scarinci G66,316/55:* In dogs, 5-HT inhibits the epilepsy produced by direct application of strychnine to, or direct electric stimulation of the brain.

Tremarine ←. *Bowman & Osuide F98,712/68:* In chickens, the toxic effects of tremarine and harmine are inhibited by 5-HT and numerous other drugs.

Tween 80 ←. *Trentini et al. G71,152/68:* In rabbits, the cholesterol-atherosclerosis-inhibiting effect of Tween 80 is diminished both by 5-HT and by norepinephrine.

Tyramine ← 5-HT: *Insocoe et al. F70,325/66*

Urethan ←. *Pierre & Cahn C24,570/55:* In rats, 5-HT prolongs thiopental anesthesia, but has no definite effect upon pentobarbital, urethan, or ether narcosis. In rabbits, 5-HT prolongs pentobarbital anesthesia but has no definite effect upon thiopental and urethan narcosis.

Vitamin D, DHT ← cf. also Selye G60,083/70, p. 429. Selye & Gentile D6,950/61: In rats pretreated with DHT p.o., selective calcification of the submaxillary glands can be obtained by 5-HT s.c. as a manifestation of calciphylaxis.

Erspamer E5,915/66: A monograph on 5-HT and related indolealkylamines, with a special section on their protective effect against radiation injury, hepatic cirrhosis produced by CCl_4 or allyl alcohol, and cardiovascular calcifications produced by DHT.

Microorganisms ←

Fishel et al. E8,474/64: Review (8 pp., 26 refs.) on the mechanism of sensitization by B. pertussis vaccine to histamine and 5-HT. The published data "indicate that the basis of this hypersensitivity is a blockade of a part of adrenergic division of the sympathetic nervous system. Preliminary experiments are also described, which suggest that a similar mechanism may also be operative in the local Shwartzman reaction."

Sellers H10,893/69: In mice, epinephrine or 5-HT injected simultaneously with various viruses i.v. enhances their infectivity and their penetration into the brain.

Bacterial Toxins ← cf. also Selye E5,986/66, p. 85.

Boroff C75,371/59: In mice, both the toxicity and ultraviolet fluorescence of Cl. botulinum toxin are inhibited by 5-HT and tryptophan, as well as by substances releasing 5-HT into the circulation (e.g. reserpine, chlorpromazine).

Gordon & Lipton C94,649/60: 5-HT reduces endotoxin mortality in mice. This effect is greater in females than in males and is potentiated by cortisol. Thyroxine aggravates the toxicity of endotoxin.

Boroff & Fleck F87,254/67: In mice, 5-HT increases resistance to botulinum toxin given 30–60 min later.

Simpson G60,451/68; H5,300/68: In mice, botulinal poisoning is prevented by 5-HT. Although both 5-HT and the toxin act upon mechanisms of cholinergic synaptic transmission, work with isolated nerve-muscle preparations showed that the synaptic junction is not the site of 5-HT and toxin interaction, suggesting "that it is the circulatory system rather than the nervous system at which the two drugs interact."

Ionizing Rays ←**MOUSE**

Bacq D77,006/54: In mice, resistance to whole body X-irradiation is increased by numerous amines, particularly cysteamine (β -mercaptoethylamine), norepinephrine, 5-HT, and histamine.

Langendorff & Koch C36,881/57: In mice, both tryptamine and 5-HT offered protection against X-irradiation, whereas amphetamine and d,L-ephedrine were ineffective.

Melching et al. C76,527/58: In mice, 5-HT i.p. increases resistance against whole body X-irradiation, but only under certain conditions of dosage and timing.

Langendorff et al. C69,396/59: In mice, 5-HT exerts a prophylactic effect against total body X-irradiation.

Semenov D7,087/60: In mice, 5-HT offers better protection against radiation sickness than epinephrine, although the latter is also effective, especially when given in combination with acetylcholine.

Doull & Tricou D4,271/61: In mice, pre-treatment with 5-HT increases resistance to whole body X-irradiation.

Feinstein & Seaholm E29,638/63: In mice, both 5-HT and the 5-HT antagonist KB-95 exhibit some radioprotective activity. Conjoint administration of both compounds is somewhat less effective than treatment with either drug alone.

Maisin et al. E36,751/63: In mice, the protection against X-irradiation offered by 2- β -aminoethylisothiourea (AET) is only slightly improved by concurrent administration of 5-HT.

Vittorio et al. D56,243/63: Review of the literature and personal observations in mice on the radio protective effect of 5-HT.

Abe & Langendorff G23,763/64: In mice, 5-HT protects the testes against damage caused by X-irradiation. The histologic manifestations of the damage and protection have been studied under varying circumstances.

Langendorff et al. G34,793/65: In mice incorporation of ^{59}Fe in the erythrocytes can be used as a test for the radioprotective effect of 5-HT, histamine, and other chemicals.

Langendorff et al. G38,385/65: In mice, an open skin wound considerably increases mortality following total body X-irradiation. After this combined treatment, 5-HT has no protective effect, whereas histamine diminishes mortality.

Kobayashi et al. G73,566/66: In mice, under suitable experimental conditions, 5-HTP offers as good, or even better, protection against whole body X-irradiation as does 5-HT.

Langendorff & Langendorff G38,396/66: In mice, the protective effect of 5-HT against X-irradiation largely depends upon the age of the animals.

Langendorff & Messerschmidt G45,424/66: In mice, the effect of 5-HT and histamine upon whole body irradiation combined with standard skin wounds is examined.

Maisin & Mattelin F78,796/67: In mice, the radioprotective effect of 5-HT can be enhanced by conjoint administration of other radioprotectors.

Cier et al. F85,815/67: In mice, the protection against total body X-irradiation given by 5-HT is considerably increased by concurrent treatment with thiosulfate. Various other radioprotective compounds offer likewise better protection and are less toxic if administered conjointly than if given singly.

Graul & Rüther G66,718/67: In mice and rabbits, 5-HT, cysteamine, and AET (β -aminoethylisothiuronium) have proved to be particularly effective as radioprotective substances against $^{60}\text{CO-}\gamma$ and X-irradiation.

Hasegawa & Landahl G48,428/67: In mice, the radioprotective effect of 5-HT depends upon the oxygen content of the air.

Maisin & Mattelin H719/67: In mice, the radioprotective effect of 5-HT is enhanced by concurrent treatment with one or more sulfhydryl compounds.

Westphal & Hagen G45,683/67: In mice, the chromosome aberrations in the thymus induced by X-irradiation are reduced by 5-HT and cysteamine.

Barnes & Lowman G63,518/68: In mice, the radioprotective effect of 5-HT can be augmented by simultaneous administration of phenelzine, a MAO-inhibitor.

Maisin et al. G59,894/68: In mice, the radioprotective effect of 5-HT can be increased by simultaneous treatment with other radioprotectors.

Streffer et al. G55,078/68: In mice, the protective effect of 5-HT against X-irradiation was compared under different experimental conditions.

Barnes & Lowman G64,917/69: In mice, 5-HT gave better protection against total body X-irradiation than did 5-HTP. Earlier claims to the contrary are not confirmed.

Léonard et al. G71,644/69: In mice, the radio-protective effect of various chemicals

given conjointly is increased by the addition of 5-HT to the mixture.

RAT

Gray et al. B92,332/52: In rats, 5-HT greatly increases survival following total body X-irradiation. The production of methemoglobinemia by para-aminopropiophenone has a similar effect; hence, the protection is ascribed to temporary tissue anoxia.

van den Brenk & Elliott C76,268/58: In rats, the protective effect of 5-HT against whole body X-irradiation is compared with that of tryptamine and other agents.

van den Brenk & Moore C71,353/59: In rats, the protective effect of 5-HT upon total body X-irradiation is reversed by breathing oxygen under high pressure.

Ladner et al. G31,673/65: In rats, 5-HT protects against whole body X-irradiation especially when combined with tryptophan.

Frölen G43,045/66: In rats "the genetic radio-protective effects of cysteamine, AET, cystamine, glutathione and serotonin have been studied. Only cysteamine showed a clear mutation-reducing effect on spermatids and spermatozoa."

Rixon & Baird G55,192/68: In rats, studies on the radioprotective effect of 5-HT suggest that intense vasoconstriction and hypoxia-induced reduction in cellular respiration may have a beneficial effect.

VARIA

Maisin & Doherty C91,781/60: A review on chemical protection against X-irradiation, with special emphasis upon the protective effect of 5-HT alone or given in combination with MEA [bis(2-aminoethyl)disulfide (cystamine)] or AET (2-aminoethylisothiourea).

Erspamer E5,915/66: A monograph on 5-HT and related indolealkylamines with a special section on their protective effect against radiation injury, hepatic cirrhosis produced by CCl_4 or allyl alcohol, and cardiovascular calcifications produced by DHT.

Koch G51,862/67: Theoretical considerations on the protective effect of 5-HT and histamine against X-irradiation.

Various Stressors ←

Hyperoxygenation ←. Laborit et al. C48,371/57; C52,731/58; C77,964/59: In mice, 5-HT protects against the convulsions produced by exposure to oxygen under high pressure.

Cold ←. Zilberstein C80,282/60: In rats, 5-HT, vasopressin, and reserpine lower resistance to cold, allegedly because they interfere with pituitary hormone secretion and cause a state of "temporary functional adrenalectomy."

Electric Stimuli ←. Scarinci G66,316/55: In dogs, 5-HT inhibits the epilepsy produced by direct application of strychnine to, or direct electrical stimulation of the brain.

de Salva et al. C51,842/58: In rats, the EST was lowered by hypophysectomy and adrenalectomy, but only insignificantly by thyroidectomy. 5-HT elevated the EST.

Sound ←. Wada et al. G48,380/67: Rats treated with methionine sulfoximine show a characteristic response to audiogenic stimuli, which is reduced by 5-HT and increased by DOPA.

Schlesinger et al. G61,802/68: In susceptible mice, audiogenic and pentylenetetrazol-induced seizures are prevented by 5-HTP, presumably because of the resulting increase in brain 5-HT concentration.

← VARIOUS OTHER HORMONE-LIKE SUBSTANCES

Prostaglandin E₁ partially protects mice against strychnine-induced convulsions.
Erythropoietin increases the resistance of mice against X-irradiation.

In dogs and rabbits, kallikrein (like other vasoactive substances) prolongs the anesthetic effect of barbiturates.

"Toxohormone" (a Walker tumor extract) allegedly causes pronounced changes in the microsomal steroidases of the rat liver.

Drugs (Var) ← cf. Selye B87,000/52, pp. 59—66, 210—216, 250, 256, 264, 269, 277, 278; B90,100/53, pp. 86—93, 267—277, 321, 322, 335, 336; C1,001/54, pp. 294—301, 451—460, 465—468, 478, 490, 491; C9,000/56, pp. 233—241, 348—352, 449—460, 470—476, 485, 486; D15,540/62, p. 275; G46,715/68, p. 176, 202.

Bacterial Toxins ← cf. Selye E5,986/66, pp. 71, 85, 86.

Stress ← cf. Selye B58,650/51, p. 50; B87,000/52; B90,100/53; C1,001/54; C9,000/56.

Varia ←

Werle & Lentzen A 28,007/38: In dogs and rabbits, various vasoactive substances (epinephrine, histamine, vasopressin, kallikrein) tend to prolong the anesthetic effect of pronarcon and hexobarbital.

Čapek D 54,290/62: In mice, bradykinin decreases the seizure threshold to strychnine, pentylenetetrazol, and electroshock. Substance P has the opposite effect.

Jones & Shapiro D 55,793/63: In rats, an acute episode of hypertension produced by epinephrine or angiotensin i.v. facilitates the production of pyelonephritis following infection with *E. coli*.

Altura et al. F 36,124/65: In rats, survival following temporary ligation of the superior mesenteric artery was improved by PLV-2, but not by epinephrine or angiotensin. The associated changes in the microcirculation of the mesoappendix are described.

Altura et al. F 43,209/65: In rats, norepinephrine and angiotensin fail to prolong survival after traumatic shock, temporary ligation of the superior mesenteric artery, or endotoxin shock. However, vasopressin (PLV-2) was significantly effective in traumatic and intestinal ischemia shock, but not in endotoxemia.

Naidu & Reddi F 80,336/67: In mice, resistance to X-irradiation is increased by erythropoietin preparations.

Duru & Türker H 10,307/69: In mice, prostaglandin E₁ partially protects against strychnine-induced convulsions.

Takahashi & Kato H 15,250/69: Studies on changes in hepatic microsomal steroidases induced in rats by treatment with "toxohormone" (a Walker tumor extract).

Vittorio et al. H 7,759/69: In mice, polycythemia induced by transfusion, increases resistance to X-irradiation. A similar result can be obtained by stimulation of stem cell activity by erythropoietin.

← TISSUE EXTRACTS

← **Hepatic Extracts.** In view of the important role played by the liver in detoxicating mechanisms, many investigations have been performed to determine whether drug resistance could be conferred by pretreatment with hepatic extracts. In rats, a certain hepatic preparation ("Yakriton") has been claimed to offer protection against a variety of toxicants. Hepatic extracts have also been said to protect the rat against methanol and its metabolites, pyruvate and acetaldehyde. Finally, rats have been protected against thyroxine intoxication by feeding hepatic extracts containing an "antitoxic factor."

← **Other Tissue Extracts.** In order to test the specificity of the acetonitrile test, mice have been pretreated with a great variety of tissue extracts; it has been found that these offer also some protection against acetonitrile, KCN and propionitrile, although they are much less efficacious than thyroid preparations. Resistance to pentobarbital anesthesia is decreased in male rats by a variety of tissue extracts (anterior pituitary, thymus, pancreas, liver, kidneys, spleen, testis, brain). On the other hand "among eight damaging agents given in doses sufficient to elicit an alarm reaction, only colchicine and atropine prolong the duration of anesthesia because of their high degree of toxicity." It remains questionable, however, whether the increase in barbiturate sleeping time produced by tissue extracts is solely due to their stressor action.

Vitamin-D₃ intoxication is largely inhibited by placenta extracts in the rat.

In frogs, fatal strychnine convulsions can be prevented if the drug is mixed with various tissue extracts prior to injection, but this may well be due to delayed absorption as a consequence of local inflammatory phenomena.

← Hepatic Extracts

Ravdin et al. B25,566/39: In rats, xanthine, allantoin, caffeine, sodium ricinoleate and suspensions of colloidal carbon injected s.c. protect the liver against injury from chloroform, presumably as a consequence of the resulting inflammatory reaction which is associated with the absorption of protein split-products. This would also explain the protective effect of various hepatic extracts (including Yakriton) and of high protein diets.

Lecoq et al. B66,406/51: In rats, the toxic effects of ethanol and its metabolites, pyruvate and acetaldehyde (which accumulate in the body under the influence of disulfiram), are inhibited by ACTH, cortisone, and hepatic extracts. Conversely, thyroxine, DOC, and testosterone appear to aggravate ethanol intoxication. [Statistically evaluated data are not presented (H.S.).]

Ershoff D5,818/61: Review of the literature, and personal observations on the protection of rats against toxic doses of thyroxine by feeding hepatic extracts containing the "antitoxic factor of liver."

Grandpierre & Robert H22,252/69: In rats, i.p. administration of a lyophilized liver extract detoxifies estradiol as judged by a diminished sex hormone activity in prepubertal animals.

← Other Tissue Extracts

Marañón & Aznar 46,926/15: In frogs, the fatal convulsions produced by strychnine can be prevented if, prior to injection, the drug is mixed with extracts of the posterior pituitary, the thyroid, various other tissues, and particularly epinephrine. [The possibility of delayed absorption owing to local vasoconstriction has not been considered (H.S.).]

Gellhorn 16,839/23: In mice, resistance against acetonitrile can be increased not only by thyroid extract, but to a lesser extent, also by extracts of various other tissues. These preparations likewise augment resistance to KCN and propionitrile, whereas thyroidectomy and orchidectomy have an opposite effect.

Masson 94,205/47: Various tissue extracts (anterior pituitary, thymus, pancreas, liver, kidney, spleen, testis, brain) as well as casein s.c. decrease resistance to pentobarbital anesthesia in male rats. On the other hand, "among eight damaging agents given in doses sufficient to elicit an alarm reaction, only colchicine and atropine prolonged the duration of anesthesia, because of their high degree of toxicity." Yet, the prolongation of barbiturate anesthesia by pituitary extracts must be ascribed to a nonspecific stressor effect.

Wietek & Taupitz C40,028/57: In rats, the syndrome of vitamin-D₃ intoxication is largely inhibited by placenta extract i.m.