Upton, L. I., New York

Two Panel Discussions on Hyperthyroidism[1,2,3]

Sidney C. Werner, Moderator

II. Etiology and Treatment of Hyperthyroidism in the Adult

DR. SIDNEY C. WERNER, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, Moderator: The second panel on hyperthyroidism is composed of the following members: Doctors Robert Conard, Carl R. Feind, Ernest Gould, David Hsia, Sidney H. Ingbar, Joseph P. Kriss, Stuart Lindsay, Farahe Maloof, J. Maxwell McKenzie, Louis Sokoloff and Kenneth Sterling.

Following the pattern of the first panel (1), we shall present a patient. But the subsequent discussion will open with two different problems: 1) the mechanism of action of thyroid hormone, and 2) the etiology of toxic diffuse goiter.

The patient was a 16½-year-old girl who arrived at the hospital with obvious hyperthyroidism of three years' duration. She also had had joint pains and fever for these three years. The hyperthyroidism had been more or less controlled with methimazole or with propylthiouracil given by various physicians. There were persistent efforts to make the diagnosis of rheumatic disease or of disseminated lupus erythematosus, but a number of rheumatologists could find no tangible evidence of either.

She had had a sore throat a few months before admission and received penicillin. After this, her joints had a flare-up of activity. She was irregular in taking her antithyroid medication and finally arrived at the hospital hyperthyroid and with evident joint involvement.

For the month prior to admission, her joint involvement had become worse; she had developed periumbilical pain associated with periods of fever to 103 F. A 24 hour radioactive iodine uptake three days after stopping the small amount of propylthiouracil she was taking was 75%.

The admission findings were as follows: She was evidently hyperthyroid, looked sick, but had no eye signs. The joints, as well as the other systems, were negative to physical examination, except for a moderate-sized rather soft diffuse goiter with a bruit. She had a fever, 103 F.

In the laboratory, 24 hour ^{131}I uptake was 55%, PBI 9 μg/100 ml. The erythrocyte sedimentation rate was 48 mm at one hour; a disseminated lupus erythematosus preparation was negative; and the antistreptolysin titer was negative.

It was concluded that she had toxic diffuse goiter; and since the usual surveys for connective tissue or rheumatic disease were essentially negative, it was considered likely that the articular and other manifestations were due to a reaction to antithyroid drugs. This view was probably correct, inasmuch as she became well when propylthiouracil therapy was terminated. The arthralgia and fever subsided.

At this point, it seemed reasonable to administer sodium iodide in preparation for surgery. Since she was 16½ years old, ^{131}I therapy was eliminated from consideration. Sodium iodide was started, 0.1 g daily. However, within 24 hours, she developed a fever of 102 F, her joints became red and swollen, and she developed a vesicular

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[3] The first of these two articles appeared in the November 1967 issue of *The Journal of Clinical Endocrinology and Metabolism*.

rash and hives over her entire body. It was finally concluded that this might be a reaction to sodium iodide and this agent was discontinued. Twenty-four hours later, her hives began to disappear, the articular signs began to clear up, and in a short time she was well again.

We were faced, then, with hyperthyroidism in a 16½-year-old girl who was allergic to the major agents used to prepare patients for surgery, for chronic medical treatment, or needed to restore euthyroidism. There followed considerable dispute as to whether operation should be performed anyway, with heavy sedation including reserpine, hypothermia, and possibly perchlorate therapy, or whether she should be treated with ^{131}I.

With this introduction, I think we can try to see what information is available which would guide us to the best conclusion. As stated, the first areas to be discussed will be the action of the thyroid hormones and the etiology of the disorder resulting in excess production of these hormones. I shall ask Dr. Sokoloff to review the former subject.

DR. LOUIS SOKOLOFF, Division of Mental Diseases, National Institutes of Health, Bethesda: Probably the earliest discovery concerning the action of the thyroid hormone was its effects on heat production and O_2 consumption (2). The timing of this discovery reflects the fact that interest in the role of the thyroid developed at a time when calorimetry, direct and indirect, was in vogue. Stimulation of metabolic rate was a very profound effect, and this early observation has dominated our thinking concerning the action of the thyroid hormones ever since. It has led to an almost continuous search for a specific effect on energy metabolism to explain the mechanism of action of the thyroid hormone.

About 15 years ago, it was found that thyroxine appeared to uncouple oxidative phosphorylation. The classic uncoupling agent, dinitrophenol (DNP), had been known to dissociate phosphorylation from electron transport and to result in increased oxygen consumption and decreased ATP formation. Since thyroxine was also a substituted phenol and was known to stimulate O_2 consumption, it was suspected that it, too, like DNP, might be an uncoupling agent. It was mainly through the work of Martins (3) and Hoch and Lipmann (4) that it was found that thyroxine does indeed depress oxidative phosphorylation. This discovery agreed with the historical bias that the thyroid hormone is primarily concerned with energy metabolism, and uncoupling of oxidative phosphorylation became widely accepted as the mechanism of action of thyroxine.

In actual fact, thyroxine does not act like DNP. Although it does depress phosphorylation and lowers the efficiency of oxidative phosphorylation, *i.e.*, lowers the P/O ratio, it generally does not stimulate O_2 consumption at the same time, at least not *in vitro*. Furthermore, if it were acting merely as an uncoupling agent, one might expect that other uncouplers might be effective in ameliorating thyroid deficiency states. They do not. Even DNP, which does stimulate the metabolic rate, has no other beneficial effect in hypothyroidism.

Also, if one considers carefully the physiological consequences of the action of the thyroid hormone, then it becomes clear that all of its multiple effects cannot possibly be explained by an effect which results in a wasting of energy, which uncoupling of oxidative phosphorylation implies. Only its effects on O_2 consumption and heat production can be so explained. The thyroid hormone, however, has many other actions, for example, its effects on growth, maturation and development, and many of these suggest increased energy utilization rather than energy dissipation. It was considerations such as these that led us to doubt that uncoupling of oxidative phosphorylation could be the specific mechanism of action of the thyroid hormone.

Our interest in the possibility that the thyroid hormone might be acting to stimulate protein biosynthesis, a process which utilizes energy rather than wastes it, first arose from observations in the nervous system, where the thyroid hormone plays an important role in maturation and development. We had been surprised to find that in adult man hyperthyroidism has no effect on the O_2 consumption of the brain (5). Actually, we should not have been surprised, for Gordon and Heming (6) had previously surveyed a variety of organs and found only three in which O_2 consumption was unaffected in hyperthyroidism, the brain, testis and spleen. It seemed to us to be more than coincidence that of these three, two, the brain and testis, have the unique characteristic of having a respiratory quotient of approximately unity (7, 8). A respiratory quotient of unity indicates that the respiratory gas exchange reflects mainly carbohydrate utilization. It appeared then that the thyroid hormone might have no effect on metabolic rate in tissues in which protein and/or lipid turnover were negligible compared to that of carbohydrate. On the other hand, in the immature brain undergoing growth and development, protein synthesis is markedly greater than in the mature brain. During this developmental period, Fazekas and co-workers (9) found that thyroxine does in fact stimulate cerebral consumption of O_2; once maturation was achieved, the oxygen consumption of the brain no longer responded to thyroxine.

It was observations such as these and many others which led us to study the action of thyroid hormones on protein biosynthesis. These investigations led to the finding that thyroxine and physiologically active analogues do indeed stimulate protein synthesis, not only *in vivo* but also when added directly to *cell*-free preparations *in vitro* (10–12). Inhibition of protein synthesis, and therefore also the effect of thyroxine on protein synthesis, by means of an agent which blocks protein synthesis, *i.e.*, puromycin, results in an immediate inhibition of the stimulation by thyroxine of O_2 consumption and restores the metabolic rate of hyperthyroid animals to the level of euthyroid controls (13). This result suggests that the effect of thyroid hormone on O_2 consumption may well be secondary to its effect on protein biosynthesis. Indeed, the effect on biosynthesis of protein with its possible consequences on the cellular levels of many enzymes might well be the basic action responsible for many of the diverse physiological and biochemical manifestations of the action of thyroid hormones.

The finding of an effect of thyroxine *in vitro* in cell-free systems from liver and other tissues has permitted studies of the chemical mechanism of the effect on protein biosynthesis. Our studies thus far clearly implicate the mitochondria in the mechanism of the effect. Thyroxine first interacts with the mitochondria to produce a soluble product or change in the soluble milieu, which in turn causes the ribosomes to increase their activity in protein synthesis (14, 15). We are currently investigating the nature and consequences of the thyroxine-mitochondrial interaction.

There is no longer any question about whether thyroid hormones stimulate protein biosynthesis. There is, however, some controversy about the mechanism of the effect. The work of Tata and his associates (16) tends to implicate an action at the gene level resulting in the increased synthesis of messenger RNA, which in turn could result in increased protein synthesis. These studies were, however, carried out *in vivo* in thyroidectomized animals. Such chronically thyroid-deficient animals have low nuclear RNA polymerase activity, and thyroid replacement therapy raises the activity back toward normal. Is this increase a cause or a consequent of other actions of the thyroid hormone? Tata claims that the effect on the RNA polymerase activity is the earliest one he observes, but his assay system does not contain mitochondria. On the other hand, we have observed with our assay system,

which contains mitochondria, that triiodothyronine administration to animals stimulates protein biosynthesis within two hours, several hours earlier than the reported effect on the polymerase activity. Also, the *in vitro* effect of thyroxine on protein biosynthesis has been observed to occur independently of any effect on DNA-dependent RNA synthesis and, in fact, in the absence of nuclei (17). The question obviously still remains to be resolved, but it is our present view that the primary effect of thyroxine is in the mitochondria, which in turn leads to increased protein synthesis, possibly also RNA synthesis, and eventually all the other consequences attributed to the hormone.

DR. WERNER: There is a recent paper in *Science* in which kidney cells in tissue culture were exposed to ^{125}I-thyroxine placed in the medium (18). The nucleus became labeled. Would this suggest that the hormone might be acting at the chromosomal or gene level?

DR. SOKOLOFF: The studies to which you refer would at first glance appear to offer evidence of an effect at the gene level and to be in conflict with our finding in cell-free systems that thyroxine stimulates protein synthesis independently of any action at the gene level but secondarily to an interaction with mitochondria. In the tissue culture studies, one is dealing with intact cells. All the cellular organelles are present, and an effect on the nuclei could conceivably be secondary to effects elsewhere. Also, in the particular studies to which you are referring (18), the added thyroid hormone was labeled with radioactive iodine, and only the radioactivity was shown to be associated to a greater degree but not exclusively with the nucleus. It may have been only the iodine or a metabolite, not the hormone itself, which was concentrated in the nucleus. At any rate, the results you refer to are certainly consistent with a possible action in the nucleus, but they can hardly be considered more than suggestive at the present time.

DR. J. MAXWELL McKENZIE, Department of Medicine, McGill University Medical School, Montreal: Dr. Werner, I would like to ask a question of Dr. Sokoloff.

Hyperthyroidism is classically a wasting disease, and if you give too much thyroid hormone to the experimental animal, there is body wasting, including depletion of protein. How does this tie in with thyroxine as a stimulator of protein synthesis?

DR. SOKOLOFF: In growing or developing animals or tissues, thyroxine may actually accelerate growth and development (9, 16, 19, 20). In the fully grown adult, it is not possible to accumulate large amounts of protein. Protein is not stored like fat. Therefore, increased protein synthesis would probably result also in increased protein breakdown. Under such circumstances, one can conceive of a cycle of increased protein synthesis and increased protein breakdown, resulting in an increased utilization of energy. I believe there is ample evidence in the literature to indicate that increased caloric intake supplemented with adequate vitamins and minerals, particularly magnesium, results in a reduction or elimination of the negative nitrogen balance or the wasting effects associated with hyperthyroidism (21, 22).

One might, perhaps, consider thyrotoxicosis as a disease characterized by an excessive or toxic stimulation of protein turnover, which results in an excessive rate of energy utilization to support this turnover. In the absence of a sufficiently increased caloric intake to meet the increased energy demand, materials normally utilized to maintain normal body structure and functions may then be drained to provide, in a sense, fuel for the toxic protein turnover; wasting then ensues. Adequate dietary intake may prevent or minimize it. It is also possible that the same mechanism

which results in stimulation of protein biosynthesis may also result in increased breakdown of protein; which direction predominates may depend on the concentration of thyroxine or other factors. The answer to this question may have to await the identification of the specific chemical mechanisms by which thyroxine stimulates protein synthesis or exerts its other effects.

DR. WERNER: I think it is only fair to say that about 15% of the patients with hyperthyroidism actually gain weight (23).

DR. McKENZIE: I have never seen a rat gain weight when it is given an excessive dose of thyroxine.

DR. WERNER: We turn now to the etiology of toxic diffuse goiter, Graves' disease. I should like to ask Dr. McKenzie to say a word about LATS, recognized to be in the immunoglobulin family, at least upon chemical separation, and about the view that this agent could act as a repressor of a repressor gene (24).

DR. McKENZIE: The point that you raise—could the IgG, long-acting thyroid stimulator (LATS), be acting as an antibody suppressing an inhibitor within the thyroid gland—has been raised in different ways by both Dr. Kriss and myself recently (24). The idea arises, of course, from the work of Jacob and Monod (25), who theorized from their work on *E. coli* that there was a genetic repressor involved in the control of protein synthesis in that organism. This concept has been applied, perhaps rather uncritically, at times, to the human organism, as a basis for explanation of the mode of action of a number of hormones. Certainly, if a genetic repressor of protein synthesis is present within the thyroid cell, then inhibition of this repressor by an antibody or by any other means might well result in unlimited or "unrepressed" synthesis of proteins which would be the enzymes and various substrates necessary for the unrestrained activity of the thyroid gland that occurs in Graves' disease.

We tested this theory by studying the effect of inhibitors of protein synthesis (puromycin and cyclohexamide) or of synthesis of RNA (actinomycin D) (24). We found that the action of both thyrotropin and the long-acting thyroid stimulator *in vivo* in the mouse was diminished when any of these antibiotics was given previously, but only if the antibiotic was given a minimum of eight to 12 hours before the thyroid stimulator. That is, there was a period of at least eight hours during which the *in vivo* thyroid synthesis of protein or RNA could be inhibited to a major degree, with no inhibition of the thyroid stimulation induced by either thyrotropin or LATS. It seemed, therefore, that the acute action of these thyroid stimulators, which is what we measure in the mouse bio-assay (26), was not dependent on the fresh synthesis of either protein or RNA, although a supply of preformed protein obviously was essential. Consequently, it seems highly unlikely that LATS could act, at least in the mouse bio-assay, by inhibition of the hypothetical genetic repressor of protein synthesis.

DR. WERNER: Dr. Hsia, would you like to say something about the etiology of hyperthyroidism from the standpoint of a geneticist?

DR. D. HSIA, Department of Pediatrics and Genetics, Northwestern University, Chicago: There appears to be little doubt that hyperthyroidism is familial, but it is not transmitted by a single gene. At least three large studies have been carried out to determine the mode of inheritance in hyperthyroidism. In 1941, Bartels (27) followed up 207 propositi from two clinics in Copenhagen. A family predisposition was found in 47% of the series as a whole, but was as high as 60% in the families where the

TABLE 1. Examination on 207 propositi with Graves' disease (28)

	Graves' disease	Simple goiter	Myxedema	Total	No. examined		Risk of development		
					Graves' disease	Simple goiter	Graves' disease %	Simple goiter %	All goiters %
Mothers	6	10	1	201	188	191	3.5	5.2	8.7
Sisters	17	23		363	213	248	8.2	9.7	17.9
Aunts	14	18	1	667	554	581	2.7	3.3	5.9
Daughters	2	8		137	22	47	9.0	17.1	26.1
Fathers				198					
Brothers	3	2		377	227				
Uncles	1			659	547				
Sons		1		169	51				

propositi showed toxic diffuse goiter. Making the necessary allowance for the inequality in sex and age distribution and estimating the risk of Graves' disease or toxic diffuse goiter by examining a control population, it was possible to assess the frequency of the gene for thyroid disease at about 12.6%. As shown in Table 1, the risk of developing goiter is greater in females, with the risk in daughters rising to 26.1%. Martin and Fisher (28) studied the families of 90 propositi with Graves' disease. As shown in Table 2, a total of 20 cases of thyrotoxicosis and 16 of simple goiter was found. The effect was more marked in Graves' disease families than in goiter families. Again the condition was seen more in female relatives than in male relatives. Finally, Boas and Ober (29) found that 11 of 143 blood relatives in five generations had exophthalmic goiter. Of this group, eight were females and three were males. From these data, it would appear that hyperthyroidism certainly was more prominent in these families, but did not follow an autosomal dominant autosomal recessive, or sex-linked mode of inheritance.

TABLE 2. Observations in 90 families with Graves' disease (28)

	Graves' disease	Toxic goiter	Simple goiter	Goiter (? toxic)	Total
Mothers		1	5		6
Fathers					0
Sisters	8	2	3	3	16
Brothers	8				8
Sons					0
Daughters				1	1
Aunts	1			4	5

It may be worthwhile to speculate on the possibility that hyperthyroidism may be transmitted on the basis of a multifactorial inheritance. Most differences between normal human beings show continuous variance. For example, if 1000 men were arranged in order of height, each would differ from his neighbor by an exceedingly small amount. Yet this variation is influenced by heredity. Continuous variation cannot be explained on the basis of single genes, but must depend on the combined action of a number of genes, or of many genes.

The regressions of child on parent, or parent on child, or sib on sib, are equal to the number of genes in common, and this is also true for more remote relationships, as shown in Table 3. Holt (30) examined the fingerprint ridge-count resemblances between relatives (Table 4) and found a good correlation with the theoretical number of genes in common. It is conceivable that hyperthyroidism represents a type of polygenic inheritance except that the condition is seen with greater frequency among females, possibly because of a hormonal effect.

DR. WERNER: If LATS is accepted as an etiologic agent, and if it is accepted that it might be an antibody, what would be found in the serum of relatives that did not

TABLE 3. Genes in common (30)

Relationship to a given subject	Proportion of genes in common
Identical twin	1
Parent, child, sib	$\frac{1}{2}$
Fraternal twin	$\frac{1}{2}$
Grandparent, grandchild, uncle, aunt, nephew, niece, half-sib	$\frac{1}{4}$
First cousin	$\frac{1}{8}$
Second cousin	$\frac{1}{32}$

have Graves' disease, on the basis of a multifactorial concept? Would one expect negative LATS titers, or would one expect a fair number of positive titers?

DR. HSIA: If one is dealing with something that is probably close to the primary gene effect, then one would expect relatives to show such changes. I don't know of any data on this subject. However, I would think that if LATS represents a fairly remote effect, then one would probably not be able to detect any such chemical consequence. It is not necessary that it appear.

DR. WERNER: Dr. McKenzie and Dr. Kriss, have you any information about relatives and LATS?

DR. JOSEPH KRISS, Department of Radiology, Standford University School of Medicine, Palo Alto: We have not done an extensive study of this point. On occasion, when we have had a LATS-positive patient, we have examined the euthyroid relatives and have not yet found a positive test in any of them.

DR. McKENZIE: Our experience has been similar to that of Dr. Kriss in this regard.

It seems that the genetic abnormality is the inheritance of a predisposition to the formation of auto-immune antibodies, of which LATS is but one. There is no doubt (31, 32) that there are many auto-immune phenomena associated with Graves' disease on a familial or inherited basis.

DR. SIDNEY H. INGBAR, Department of Medicine and Thorndike Memorial Laboratory, Boston City Hospital, Boston: In relation to the LATS problem and the genetic implications of some unpublished observations that Dr. Freinkel and I made a number of years ago, one thing that confuses me is that, in studying the thyroid function in a group of relatives of patients with active diffuse toxic goiters, we found about 20% with elevated thyroidal uptakes of ^{131}I. When we analyzed the nature of the relationship of increased uptake relative to the patient, the result was much the same as Dr. Hsia suggested it might be. Siblings showed a higher incidence of abnormal uptakes. However, virtually all of these patients showed suppressible thyroid function with exogenous hormone. I am not quite sure we can equate the presence of LATS with lack of suppression, but possibly we can. I would like to think that might be the case, and therefore we asked ourselves why the uptakes were elevated in this 20% of relatives, in the absence of LATS.

The other surprisingly frequent finding was that there was some disturbance of turnover of thyroxine peripherally. Many of the relatives had an accelerated turnover rate with half-times of $4\frac{1}{2}$ to five days,

TABLE 4. Fingerprint ridge counts: resemblances between relatives (30)

Relationship	No. of pairs	Observed correlation	Theoretical correlation
Identical twins	80	0.95 ± 0.01	+1.0
Fraternal twins	92	0.49 ± 0.08	+0.5
Sib-sib	642	0.49 ± 0.04	+0.5
Parent-child	602	0.50 ± 0.03	+0.5
Husband-wife	149	0.05 ± 0.08	0

which we would consider to be distinctly rapid. A number of these relatives now—this was about ten years ago—have become thyrotoxic and have developed nonsuppressible thyroidal function. But they had abnormalities in iodine metabolism beforehand.

DR. WERNER: I want to ask Dr. McKenzie a question. One of the evidences which has been cited to show that LATS may be the etiologic factor of Graves' disease is the fact that it is present in the neonate, born of a hyperthyroid mother, and then disappears as the baby recovers. Now I understand your comments to indicate that you don't think that LATS is a primary factor in this disorder.

DR. McKENZIE: The concept I have at present is that LATS is a primary factor in the pathogenesis of the hyperthyroidism of Graves' disease; regarding the etiology of the syndrome, however, I think we should consider that a genetic abnormality in immune tolerance, or a predisposition to the formation of autoantibodies, is a primary inherited factor. I certainly would not suggest that Graves' disease is LATS and nothing else.

DR. KRISS: There are two other bits of evidence that might be mentioned here with respect to genetics. Dr. Mosier has reported finding LATS in the sera of some infants with mongolism. Tied in with that is Fialkow's observation that infants with mongolism and their mothers have a higher incidence of antithyroglobulin antibody, and the mothers have a higher incidence of Hashimoto-type thyroiditis.

Fialkow (33) is inclined to the view that the antibodies perhaps caused the chromosomal abnormality. We could conceive of an abnormality in a chromosome as having something to do with a subsequent abnormality of the thyroid in children. Then, LATS might be thought of as arising from a form of genetically induced injury. Despite the presence of LATS, the infant with such a damaged gland may remain euthyroid.

DR. WERNER: I don't suppose one should quote unpublished data, but we obtained serum from four patients with mongolism at Letchworth Village and found no LATS in any.

We should now go on to a recent observation by Dr. Helen Farran (34) which seemed quite interesting to me. When she fed tyrosine to patients with hyperthyroidism, she found that the serum PBI concentration rose. Dr. Farran attributed the increase in PBI to increased formation of iodotyrosine.

DR. McKENZIE: Can we invite Dr. Werner to enlarge on that point?

DR. WERNER: It is known that plasma tyrosine levels become elevated after feeding of tyrosine to hyperthyroid patients or normal subjects after administration of triiodothyronine (35). Farran and Shalom (34) found that there is also an increase in serum PBI, due, they claim, to an increase in circulating iodotyrosines. The latter were separated by a fractionation method not yet published. The change in PBI was highly significant in three of the eight hyperthyroid patients. Unfortunately, the demonstration of the presence of iodotyrosines in serum in hyperthyroidism has been based on single dimension chromatographic procedures, and has not been confirmed by more sophisticated techniques, as far as I know.

We come to the next point, the role of the liver in the degradation of thyroxine, and the importance of the enterohepatic circulation of thyroid hormone in man, and its influence on the levels of serum thyroxine and thyroid hormone conjugates.

I shall ask Dr. Ingbar if he would want to say something about this, and Dr. Sterling.

DR. INGBAR: I am not sure that we know to what extent an enterohepatic circula-

tion does exist in man. Certainly, it has been shown that if you have a patient with a tube in the bile duct and give thyroxine, a certain amount will come out in the bile, in the form of both conjugated and unconjugated T_4. Only very cursory attempts have been made, but, certainly, no thyroxine binding substance is present in human bile. To what extent the thyroxine may be reabsorbed, I am not certain, because I don't think, when one has a tube in a bile duct, one can conclude that the quantity of thyroxine entering the bile is the same as that which would enter if the patient did not have a tube in the bile duct. Also, there are abnormalities in normal binding which occur in sick patients which might influence hepatic uptake and secretion, but I have no basis for an accurate estimate of this.

DR. KENNETH STERLING, Department of Medicine, Bronx Veterans Administration Hospital, New York: Our information in man is limited. It appears that, in experimental rats, the amount of thyroxine conjugated as glucuronide and the amount of T_3 conjugated as sulfate are quite appreciable. It appears to be less in human subjects. I don't doubt that the phenomenon has clinical significance in states of hepatic impairment. We do know in thyrotoxicosis that there may be impairment of liver glycogen stores. I think, however, this is more for future investigation than for present comment.

DR. INGBAR: There is no evidence that the proportion of hormone that comes out in the stool of thyrotoxic patients is appreciably different than in euthyroid patients. Of course, the quantity coming out is larger, but the proportion is not different. Thus, this does not suggest that there exists some detoxifying or excretory mechanism of particular physiological importance.

DR. WERNER: The liver is subject to a degree of functional injury in hyperthyroidism, as shown by decrease in serum albumin and rise in serum globulin, as well as by a change in BSP excretion. Is it possible, with increasing liver damage, that there might then occur a change in function of the enterohepatic circulation?

DR. INGBAR: Swiss workers found that there was an element of this in patients with acute, severe liver disease, acute viral hepatitis, as I recall. They suggested there was evidence of diminished conjugation in the biliary secretion.

DR. WERNER: Could this result in backing up, with a rise in the level of total and hence of free thyroxine?

DR. INGBAR: It would raise the PBI, but whether this is due to a backing up phenomenon is not clear because they found that thyroxine binding globulin was increased. I am sure they didn't have any direct measurements of free thyroxine.

DR. McKENZIE: I could add that we found in various disorders of the liver, mainly cirrhosis, TBG can be elevated. In at least one of the patients, we made independent studies which showed a high circulating level of estrogen, so that the TBG may be elevated on this account. TBG may also be markedly diminished, however, and not infrequently TBPA may be diminished, so a variety of changes can occur with injury to the liver.

DR. WERNER: TBPA levels decrease in liver disease. Therefore, does the increase in TBG level indicate that there is a reciprocal relationship between the two proteins, and, if so, how is a change in one protein detected by the regulatory mechanism for the other?

DR. McKENZIE: I would say that, except for hepatic disease, one sees a reciprocal relationship under most circumstances. Dr. Braverman and Dr. Ingbar have shown that in normal males and

females there is a difference, and that the females have a higher TBG than males, and one can plot graphs showing this reciprocal relationship, and I think, Dr. Werner, you showed—and later with Dr. Oppenheimer—that administration of steroids gives rise to elevation of TBPA and diminution of TBG. The same thing can occur in acromegaly. In hepatic disease, on the other hand, apparently because of failure to synthesize these proteins, the normal reciprocal relation fails to hold. We don't really know, although we are inclined to guess that TBPA may possibly be primary in this relationship, but it is very hard to say at this stage.

DR. WERNER: Lest the patient problem be lost in the discussion of pathogenetic mechanisms, I shall ask Dr. Maloof to say a word about the metabolism of some of the major antithyroid drugs and something about the mechanism of sensitivity to such agents. I shall then ask Dr. Conard to say a word about ^{131}I radiation effects on the thyroid.

DR. FARAHE MALOOF, Department of Medicine, Massachusetts General Hospital, Boston: The metabolic studies we have carried out with the antithyroid drugs, primarily thiourea, have shown clearly that this drug is taken up by the thyroid in small amounts, about 1% of the administered dose/g thyroid, and that it is specifically metabolized by thyroid tissue (36). We have on the basis of our studies postulated a mechanism of action by which thiourea inhibits the iodination reaction (37).

I think, to go back to the first panel (1) discussion, in which everybody stated that the antithyroid drugs passed through the placenta, this may not be completely valid because the only studies that have been done have been those with thiourea (38). Shepard demonstrated clearly that thiourea did go through the placenta of the rat and was taken up and metabolized by the fetal rat thyroid. Whether this applies to other antithyroid drugs remains to be seen.

Another point in regard to this problem is that, in animals given thyroxine, the uptake of the thiourea by the thyroid is greatly diminished. I suppose that someone, some day, should do this experiment in pregnant rats to see whether the administration of thyroxine to the mother suppresses the transmission of the antithyroid drugs by the placenta, and hence suppresses the uptake by the fetal thyroid. This may have a very important bearing on the method which Herbst and Selenkow have advocated for treating pregnant women with hyperthyroidism, namely, thyroid along with antithyroid drugs in order to inhibit a fetal goiter (39, 40).

None of the work that we have done would help in elucidating the mechanism by which these drugs produce sensitivity in some patients.

DR. WERNER: Is there an explanation for hypersensitivity to sodium iodide? Allergic reactions of this magnitude have been recognized since early days.

DR. INGBAR: Is there some special reason why you say iodide? That is what is given to the patient, but that is not necessarily what is producing the reaction. We know that if we give large doses of iodide to patients, there are iodinations which occur—probably iodinations of serum proteins, and perhaps other proteins. I think there are data in the immunologic literature which suggest that such iodinated protein does not have specific immunologic properties and that there is a good deal of cross-reaction between a variety of iodinated proteins. This was studied a number of years ago. For example, antibodies to iodinated diphtheria toxin would react with iodinated albumin. Iodinated protein, certainly, is a good antigen, and hence there

is no reason to doubt that what we see in patients who are allergic to iodides is the action of an iodoprotein formed in these patients.

We do know that hyperthyroid patients make iodinated proteins of this type, and release them into the circulation; and, to some extent, there is a cross relation between a variety of such iodinated proteins. Thus, if patients with Graves' disease produce a spectrum of antibodies against thyroproteins, some of which are iodinated proteins, it might not be surprising that some patients with this disorder would show allergic reactions to iodine.

DR. WERNER: We ought to discuss, briefly, ^{131}I. Dr. Conard from the Brookhaven National Laboratories has been involved with the Marshallese fallout problem together with Dr. Rall. I wonder if he would like to say something about radiation effects from this isotope upon the thyroid.

DR. ROBERT CONARD, Brookhaven National Laboratories, Upton, New York: Until relatively recently, the thyroid gland had always been considered a rather radioresistant organ. However, in the past few years it has become apparent that the gland is more radiosensitive, particularly in regard to late effects, than had been thought. This applies both to external and internal radiation of the gland.

Radiation may affect the thyroid cells in several possible ways: by directly killing the cells, by injuring the genetic mechanism so that at the time of cell division the cell may die or a mutant form may persist, or radiation may simply impair the function of the cells. Chromosomal aberrations have been demonstrated in irradiated thyroid cells and numerous histological changes in thyroid tissues have been noted following irradiation. These are characterized by cellular necrosis, nuclear changes, fibrosis, blood vessel changes, etc.

There have been many animal studies showing functional and neoplastic changes in the thyroid as a late effect of radiation. More recently, there have been a number of both retrospective and prospective studies in human beings. It has been clearly established that infants who receive neck irradiation later develop a higher incidence of cancer of the thyroid gland (41, 42). There appears to be an increase in cancer of the thyroid in the Japanese people that were exposed to the atomic bomb radiation (43). As for internal exposure of the thyroid gland, the development of thyroid nodules and possibly one case of malignancy have been noted in children, years after receiving radioiodine therapy for hyperthyroidism (44). Also, in recent years, an increasing number of cases of hypothyroidism are being reported following such treatment in adults.

The recent development of thyroid nodules in the Marshallese has been of particular interest. We carry out annual medical examinations of 86 people who were accidentally exposed to radioactive fallout 12 years ago, in 1954. Most of these people received an estimated dose of 175 rads of whole body γ-radiation, β-burns of the skin, and internal absorption of radioisotopes. During the two days before they were evacuated from their island, they absorbed significant amounts of radioiodine from consumption of contaminated food and water. Estimates of thyroid dose were arrived at by radiochemical analyses of the urine done at 15 days and longer after exposure. It was estimated that the adults received about 160 rads from radioiodines plus the 175 rads of γ-radiation to the gland. The children, having smaller glands, naturally received larger doses per unit weight of gland. A three- to four-year-old child was estimated to have received between 700 and 1400 rads from radioiodines plus the external gamma dose.

About three years ago, we first noticed the development of nodules of the thyroid gland in these people (40, 45, 46). Since that time, the incidence has increased un-

til we now have 18 cases of thyroid pathology. Seventy-nine per cent of these have occurred in children that were exposed at less than ten years of age. Eleven patients have been operated upon and, of the 11, nine were children, all showing benign adenomatous goiter histologically rather than the type one sees with iodine deficiency. However, there is no iodine deficiency in the Marshall Islands where they live, and no known goitrogenic foods exist there. One case of cancer has developed in one of the three adults with nodules. This was in a 41-year-old woman and was of the mixed follicular and papillary type with localized metastases in lymph nodes and blood vessels.

Another interesting aspect of the study is the possible relationship of the thyroid pathology to the slight degree of retardation of growth and development that has been noted over the past years in the exposed children (47). In the last three years, frank hypothyroidism has occurred in two boys who have shown the greatest retardation of growth. Their PBI values dropped below 2 μg/100 ml, and they showed all the characteristics of hypothyroidism. In addition, several other children have had low PBI values. It thus appears that this growth retardation may well be related to the effects of radiation upon the thyroid gland. We had not suspected the thyroid relationship in earlier years, since PBI levels had appeared to be normal. As a matter of interest, the Marshallese have considerably higher PBI levels than Americans. Dr. Rall and I, in studying this, have found that there was a high level of iodoprotein which largely accounted for the high PBI values (48). Therefore, it seems likely that earlier detection of thyroid hypofunction in these children may have been masked by the finding of falsely normal PBI levels.

Thus it appears, as a result of these developments in the Marshallese and other studies which I have referred to, that the thyroid gland is not as resistant, particularly to late effects of radiation, as had been supposed previously. In view of this, it would seem that we must seriously consider the hazard associated with the use of radioiodines in the treatment of thyroid disease, particularly in children.

DR. WERNER: Dr. Lindsay, it is common knowledge that, if one operates on enough patients with hyperthyroidism, a fair number of them will have thyroid cancer instead of the seeming toxic diffuse goiter, or may have cancers within the hyperthyroid gland. Yet there has been a sharp decrease from the expected incidence of thyroid cancer in patients treated with ^{131}I. I wonder if you would like to speculate about this.

DR. STUART LINDSAY, Department of Pathology, University of California Medical Center, San Francisco: In any series of patients with Graves' disease who are operated upon, a certain number, probably something less than 1%, will be found to have microscopic carcinomas, usually papillary in type. I have seen several of these which were probably of multicentric origin.

This finding always brings up this question. If a thyroid carcinoma should appear later in a patient with Graves' disease who had been irradiated with ^{131}I, was the neoplasm really an effect of radiation or was it possibly a tumor that had been present before the ^{131}I radiation? This is a point that is at present impossible to answer.

DR. MALOOF: I would like to ask Dr. Conard to clarify the problem of ^{131}I irradiation and cancer of the thyroid reported to be found in children exposed to radiation in the Marshallese Islands (46).

I would like to make one point about this. In the paper by Dr. E. M. Chapman and myself in 1955 (49), we reported that there was no greater incidence of thyroid cancer in our patients with hyperthyroidism who had been given ^{131}I than in other

groups of hyperthyroid patients treated by surgery or antithyroid drugs. I am wondering whether there is any concrete evidence that radioiodine therapy produces cancer or will produce cancer of the thyroid.

DR. CONARD: Though we have only one case of cancer of the thyroid in the exposed Marshallese group, one has to consider the possibility that this is related to radiation exposure, particularly since the incidence of such malignancy is apparently quite low in the Marshall Islands, something like two cases in 15,000 people in ten years. I think the statistics are in favor of this case being radiation-induced, though there is no certainty of it. One must also consider the apparent increase in thyroid cancer in the exposed Japanese adults.

In answer to the question about the normal PBI values we reported, it should be remembered that these values were obtained early in our studies, and at that time hypothyroidism may have been borderline. Later, when definite signs of hypothyroidism developed, the blood thyroxine levels became clearly low.

DR. WERNER: Perhaps we can now deal more directly with the therapy of our patient, 16 years old and allergic to antithyroid drugs and iodides. Dr. Sterling.

DR. STERLING: It seems to me, offhand, that there are three possible choices of treatment. One is immediate surgery, another, radioiodine therapy, and the third might be—even though she has a sensitivity to these drugs—propylthiouracil and iodide. One might give her sodium perchlorate, which I have used with success in people sensitive to all the other medicaments. I have seen one patient who was sensitive to perchlorate, as well. I would be tempted to give perchlorate under careful observation in the hope of rapidly preparing her for subtotal thyroidectomy.

DR. WERNER: I had originally planned to suggest surgery on the ground that surgery could be carried out with a minimum risk of hypothyroidism. However, we have discovered in reviewing the experience at our hospital—and I see Dr. Beierwaltes has discovered this at his hospital, also (50)—that the surgeons have been doing almost as good a job in producing hypothyroidism as those of us who use ^{131}I. Each year from the 1940's when our surgical rate of hypothyroidism was around 3 to 6%, there has been a progressive rise in the postoperative incidence of hypothyroidism, so that now the incidence is in the range of 30%. This statistic removes some of the relative value of surgery over ^{131}I. However, the trend is not an irreversible one, whereas so far, at least, the high incidence of hypothyroidism in ^{131}I therapy seems to be essentially inescapable despite major efforts.

The surgeons, represented by Dr. Feind and Dr. Gould, will want to speak about this.

DR. CARL R. FEIND, Department of Surgery, Columbia University College of Physicians and Surgeons, New York: In 1940, the surgeons were treating almost all of the thyrotoxic patients. For the past ten years, the only ones that we have been treating are those that have been referred to us for very specific reasons. These are patients who did not tolerate antithyroid drugs, or who had glands that were not treated with ^{131}I for other reasons. Most such patients were younger people in their reproductive period. The surgeon, in treating a select group like this, should tend to overshoot at operation, because, if he leaves too much gland behind, he has a patient who has persistent or recurrent toxicity and is still in the same situation as when he was originally referred.

Thyroid is given after subtotal thyroidectomy, as is done after treatment with ^{131}I. In fact, most patients who are receiving antithyroid drugs are also given tri-

iodothyronine. As I said, we are now operating on a select group, and to misjudge and leave too much thyroid behind would be a grave error.

DR. ERNEST A. GOULD, Department of Surgery, Washington Hospital Center and George Washington School of Medicine, Washington, D.C.: If I had my choice here, I would rather be left with a little remnant of thyroid gland that hadn't been affected by radioactive iodine than have all of my gland and have to wait to see whether myxedema will ensue or not.

Dr. Werner, my feeling about this patient is, medical treatment has had its chance; now let us give definitive treatment. This patient can be handled readily and rapidly, and the treatment will be terminated. Now, I have no argument with those who want to talk about hypothyroidism after surgery in these people. In agreement with Dr. Feind, I would much rather make these people mildly hypothyroid. As a matter of fact, this is the goal, I think, in good surgery of hyperthyroidism today, because the replacement of thyroid hormone is so easily done. Certainly, in a patient who has already been treated for three years, who has questionable rheumatic heart disease, which may be of considerable importance later, I should think removal of the one known stress on the myocardium of this patient is terribly important. Thus, I would certainly have urged that this patient be prepared and promptly operated upon with hypothermia. I know that Dr. Sterling is skillful with perchlorate, but, again, what are we gaining by suboptimal treatment of a patient who, after three years, cannot be brought into a euthyroid state and kept there?

DR. KRISS: I am not convinced we have diagnosed this patient. We have diagnosed hyperthyroidism, but the question of all the other symptoms that have been present here raises doubts in my mind as to whether everything can be ascribed to hyperthyroidism. If I referred the patient to a surgeon, I might ask him to do a muscle biopsy, rather than a thyroidectomy.

DR. WERNER: Well, to give our own reasoning, we chose ^{131}I as the method of therapy. Surgery without an antithyroid drug or other preoperative medication and only hypothermia as preparation exposes a young patient to the risk of storm and death. Besides, we doubted that she had rheumatic or other connective tissue disease, after her dramatic recovery when medication was stopped, and after the return of symptoms with iodides. We excluded perchlorate to prepare for surgery, or chronically, since perchlorate may produce aplastic anemia, among other things. She has become euthyroid since her ^{131}I treatment and is perfectly well today, without myalgia, arthralgia or fever.

I just want to make one final comment. According to a recent statistical bulletin of the Metropolitan Life Insurance Company, mortality from toxic goiter decreased almost 90% since 1941, whereas mortality from thyroid cancer showed only minor fluctuations. In the light of our discussion, the factors responsible for these results need to be brought out, since they bear heavily on choice of therapy in hyperthyroidism.

Summary

A case history was presented of a 16-year-old girl with hyperthyroidism. She had been chronically treated with antithyroid drugs for 3½ years but throughout this same period of time manifested fever and joint pains. Subsequent discussion presented a review of the evidence concerning the primary action of thyroid hormone within the cell; a survey of the nature of the pathogenesis and etiology of Graves' disease; and a discussion of radiation effects on the thyroid cell. There then followed a debate as to the proper method of treatment of this patient and of hyperthyroid patients in general. It was pointed out that the high incidence of hypothyroidism after

^{131}I therapy is currently being equaled by operation, presumably due to more aggressive surgery. Whether reversion to a more limited surgical procedure would result in a balance favoring surgery over ^{131}I in this respect, or whether success of newer efforts to limit the hypothyroidism rate post-^{131}I therapy would tilt the balance toward ^{131}I, was not settled. Most but not all the participants were against operative therapy for the patient under discussion. She had been, in fact, successfully treated with ^{131}I.

References

1. Hyperthyroidism in the pregnant woman and the neonate, *J Clin Endocr* **27:** 1637, 1967.
2. Magnus-Levy, A., *Klin Wschr* **32:** 650, 1895.
3. Martins, C., and B. Hess, *Arch Biochem* **33:** 486, 1951.
4. Hoch, F. L., and F. Lipmann, *Proc Nat Acad Sci USA* **40:** 909, 1954.
5. Sokoloff, L., R. L. Wechsler, R. Mangold, K. Balls, and S. S. Kety, *J Clin Invest* **32:** 202, 1953.
6. Meyer, A. E., C. M. Stickney, D. Marine, and J. Lerman, *Endocrinology* **34:** 347, 1944.
7. Kety, S. S., Metabolism of Nervous System, Pergamon Press, London, 1957, p. 221.
8. Macht, D. I., A. E. Stickels, and D. L. Seckinger, *Amer J Physiol* **88:** 65, 1929.
9. Fazekas, J. F., F. B. Graves, and R. W. Alman, *Endocrinology* **48:** 169, 1951.
10. Sokoloff, L., and S. Kaufman, *Science* **129:** 569, 1959.
11. ———, *J Biol Chem* **236:** 795, 1961.
12. Michels, R. J., J. Cason, and L. Sokoloff, *Science* **140:** 1417, 1963.
13. Weiss, W. P., and L. Sokoloff, *Science* **140:** 1324, 1963.
14. Sokoloff, L., Proc. 2nd Int. Congr. Endocr., Exerpta Med., Amsterdam, Series 83, 1964, p. 87.
15. Sokoloff, L., P. L. Campbell, C. M. Francis, and C. B. Klee, *Biochim Biophys Acta* **76:** 329, 1963.
16. Leaf, A., Proc. 2nd Int. Congr. Endocr., Exerpta Med., Amsterdam, Series 83, 1964, p. 72.
17. Sokoloff, L., C. M. Francis, and P. L. Campbell, *Proc Nat Acad Sci USA* **52:** 728, 1964.
18. Siegel, E., and C. A. Tobias, *Science* **153:** 763, 1966.
19. Eayrs, J. T., *Arch Biol (Liege)* **75:** 529, 1964.
20. Wilkins, L., The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, ed. 2, Charles C Thomas, Springfield, Ill., 1957, p. 137.
21. Boothby, W. M., and I. Sandiford, *JAMA* **81:** 795, 1923.
22. Vitale, J. J., D. M. Hegsted, M. Nakamura, and P. Connors, *J Biol Chem* **226:** 597, 1957.
23. Werner, S. C. (ed.), The Thyroid, ed. 2, Harper & Row, New York, 1962, p. 494.
24. McKenzie, J. M., *Recent Progr Hormone Res* **23:** 1, 1967.
25. Jacob, F., and J. Monod, *J Molec Biol* **3:** 318, 1961.
26. McKenzie, J. M., and A. Williamson, *J Clin Endocr* **26:** 518, 1966.
27. Bartels, E. D., Op. Dom. Biol. Hered. hum. Kbh. 2, Munksgaard, Copenhagen, 1941, p. 384.
28. Martin, L., *Quart J Med* **14:** 207, 1945.
29. Boas, N. F., and W. B. Ober, *J Clin Endocr* **6:** 575, 1946.
30. Holt, S. B., *Brit Med Bull* **17:** 247, 1961.
31. Anderson, J. R., K. G. Gray, D. G. Middleton, and J. A. Young, *Brit Med J* **11:** 1630, 1964.
32. Saxena, K. M., *Lancet* **1:** 583, 1965.
33. Fialkow, P. J., F. Hecht, I. A. Uchita, and A. G. Motulsky, *Lancet* **2:** 868, 1965.
34. Farran, H. E. A., and E. S. Shalom, *J Clin Endocr* **26:** 918, 1966.
35. Melmon, K. L., R. Rivlin, J. A. Oates, and A. Sjoerdsma, *J Clin Endocr* **24:** 691, 1964.
36. Maloof, F., and M. Soodak, *Endocrinology* **61:** 555, 1957.
37. ———, Proc. of the 5th Int. Thyroid Conf., Rome, 1965, Acad. Press, New York, p. 277.
38. Shepard, T. I., II, *Endocrinology* **72:** 223, 1963.
39. Herbst, A. L., and H. A. Selenkow, *Obstet Gynec* **21:** 543, 1963.
40. ———, *New Eng J Med* **273:** 627, 1965.
41. Duffy, B. J., Jr., and P. J. Fitzgerald, *Cancer* **3:** 1018, 1950.
42. Simpson, C. L., L. H. Hempelmann, and L. M. Fuller, *Radiology* **64:** 840, 1955.
43. Socolow, E. L., A. Hashizume, S. Neriishi, and R. Niitani, *New Eng J Med* **268:** 406, 1963.
44. Sheline, G. E., S. Lindsay, K. R. McCormack, and M. Galante, *J Clin Endocr* **22:** 8, 1962.
45. Conard, R. A., and A. Hicking, *JAMA* **192:** 457, 1965.
46. Conard, R. A., J. E. Rall, and W. W. Sutow, *New Eng J Med* **274:** 1391, 1966.
47. Sutow, W. W., R. A. Conard, and K. M. Griffith, *Pediatrics* **36:** 721, 1965.
48. Rall, J. E., and R. A. Conard, *Amer J Med* **40:** 883, 1966.
49. Chapman, E. M., and F. Maloof, *Medicine (Balt)* **34:** 261, 1955.
50. Nofal, M. M., W. H. Beierwaltes, and E. Patno, *JAMA* **197:** 605, 1966.