occurs after fires, after explosions due to coal dust or gases, and after the use of explosives; and in smelters about the preroasters, roasters, blast furnaces, flues and bag houses. We also find it about petroleum refineries. While I do not minimize the great danger of this gas, I do want to emphasize what seems to me an unwarranted amount of fear or hysteria regarding it. Dr. Henderson has called your attention to this. Both men and animals develop a partial tolerance to this gas after having been exposed to increasing amounts over a considerable period. Dogs have developed sufficient tolerance to have no bad effects after exposure for several hours to 0.8 per cent. Recently I have seen a partial tolerance in a canary bird which we were using in some experiments. This canary can stand fully twice the concentration of a bird not previously exposed. After exposure of two hours to 0.16 per cent., it was active and able to hop from its perch to the bottom of the cage and back again, while an analysis of my own blood, I having remained with the bird the entire time, showed the blood to be 47 per cent. saturated with the gas. Continuing these experiments on myself, I remained on other days in the gas sufficiently long to produce a saturation of from 36 to 40 per cent., after which, for the elimination of the carbon monoxid, breathing pure oxygen was compared with the breathing of a mixture of about 9 per cent. carbon dioxid, 89 per cent. oxygen, and 2 per cent. nitrogen. The oxygen-carbon dioxid mixture increased the lung ventilation from 300 to 400 per cent. over the normal. Oxygen (98 per cent.) produced no increased lung ventilation. The carbon monoxid was eliminated from the blood rather rapidly during the first ten or fifteen minutes with the use of either; but some carbon monoxid could be found in the blood for five or more hours later, but could not be detected after twenty-four hours. The mixture or the pure oxygen was breathed for forty-five minutes on each test. We are trying the two methods on dogs after sufficient exposure to cause profound unconsciousness, but this work is not completed. At the present stage of our experiments for the conscious man poisoned by carbon monoxid, the breathing of pure oxygen seems to give better results as to relief of symptoms and almost as rapid elimination of carbon monoxid from the blood as does the carbon dioxid-oxygen mixture.

DR. YANDELL HENDERSON, New Haven, Conn.: I can guarantee, from my own experience, that although we talk a little lightly about carbon monoxid, to get one's blood 47 per cent. saturated, as Dr. Sayers did, is an experience which one does not want to undertake lightly. It is heroic. It takes a man of great equilibrium and sweet temper to do it and still be tolerant toward the paper he is to discuss. With regard to the oxygen-carbon dioxid apparatus, it is virtually an oxygen inhaler somewhat like that used in the Bureau of Mines for gassed miners. It is important to be economical of oxygen, because you cannot carry a great many cubic feet. Once you stimulate respiration it uses up oxygen pretty fast. The apparatus is now being tested out at the Bureau of Mines Experiment Station in Pittsburgh. It was developed originally for the treatment of soldiers gassed with the irritant war gases in France, but the war came to an end before it came into use. A question has been asked me with regard to the lung motor, the pulmotor and other mechanical apparatus. The standpoint which seems to me to be justified now by eight years of experience, since the first commission investigated the matter, is that even if we had an ideally perfect apparatus for giving artificial respiration, it would still be better to discourage, and even to forbid the manufacture, sale, use and introduction of such apparatus, because it leads to delay, and thus to more deaths—deaths which could and should be restorations. If a man is drowned to the point at which he has stopped breathing, and his heart is beating only feebly, or if a man has gotten hold of a live wire and his respiration has stopped, you have often only two or three minutes within which life can be restored. Now, it is impossible for us all to go around with a lung motor or any other apparatus strapped to our backs all the time: hence an often fatal delay. Laboratory experience shows also that for most cases the manual method is actually better. Dr. Meltzer was strongly of the opinion, and I think he was justified, that mechanical apparatus very often injures the lungs seriously. On the other hand, the manual, or Schäfer method has a large number of clear cut recoveries to its credit. The supremely important point, as experience proves, is that you cannot have people prepared to give the manual method, and you cannot introduce routine training, if they know that when they telephone for a lung motor or pulmotor, it will come. I am more and more strongly of the opinion that the introduction of apparatus actually increases fatalities.

THE PREVENTION OF SIMPLE GOITER IN MAN*

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Simple or endemic goiter is one of the most benign and insidious diseases of man and animals. The sum total of its ravages throughout all ages and in all lands is still unrealized by the public generally, notwithstanding the numerous reports of commissions appointed for its study. Those who live on the sea coasts fortunately have had no need to be concerned; and those who lived in goiter districts—before the days of extensive travel—grew accustomed to look on goiter as natural and normal. Indeed, in many districts of the world, it is still looked on as a mark of beauty.

Simple goiter includes all those thyroid enlargements in man and animals formerly grouped as endemic, epidemic, sporadic and physiologic. It must be sharply distinguished from exophthalmic goiter, with which it has no necessary association or etiologic relationship. Exophthalmic goiter, so far as is yet definitely known, occurs spontaneously only in man, while simple goiter occurs in all animals having the ductless thyroid. Exophthalmic goiter is not notably associated with districts, while with simple goiter this is most characteristic. Exophthalmic goiter occurs more frequently in the highly developed and civilized races, while in simple goiter race is not a factor. Simple goiter may develop sporadically in any place (even at sea, as reported on one of Captain Cook's voyages), but it is preeminently associated with certain regions or districts. The distribution of these districts of endemic goiter throughout the world was fully described by Hirsch, in 1860. The actual incidence of goiter within a given district is still quite unknown. With the information at present available, however, one can distinguish between mildly and severely goitrous districts. As compared with certain other districts, for example, the Alps and the Himalaya regions, our most important districts, namely, the Great Lakes Basin and the Cascade Mountain regions of Oregon, Washington and British Columbia, would be classified as mildly goitrous. The mildness or severity of a district may be determined by the incidence of myxedema or cretinism—a fact known to Morel and expressed in his famous dictum, "Goiter is the first halting place on the road to cretinism" (Le goitre est la première étape sur le chemin qui conduit au cretinisme).

ETIOLOGY

The ultimate cause of simple goiter is totally unknown, notwithstanding a relatively large amount of study. The immediate cause is a lack of iodin. The

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enlargement, therefore, is a symptom and may result from any factor which increases the iodin needs of the organism, as in certain types of infection, or which interferes wtih the normal utilization of iodin; or it may result from actual experimental deprivation of iodin. The conception that it is due to a contagium vivum in the sense that this term is ordinarily used may be abandoned. Water has been associated as an etiologic factor by all peoples as far back as history goes. The American Indians (Barton) and the natives of Central Africa (Livingston) seem to have been as strongly convinced of the relation of water to the disease as was Hippocrates. If water is a factor, it would seem that it is the absence rather than the presence of some substance, which is to be considered, since goiter is associated with the purest of waters, chemically and bacteriologically as, for example, in Portland, Ore., and in Seattle and Tacoma, Wash., where there has been a rapid increase in goiter since these cities began to take their water supplies from the Cascade Mountains. After consideration of all the various substances, agents and theories that have been put forward as having a rôle in the etiology of goiter, we at present must fall back on the view that thyroid hyperplasia (goiter) is a compensatory reaction arising in the course of a metabolic disturbance and immediately depending on a relative or an absolute deficiency of iodin.

PATHOLOGIC ANATOMY

Anatomically, a wide range of changes may be present, depending on the species of animal and on the stage (duration) of the disease. It always begins with a decrease in the colloid material and a hypertrophy of the epithelial cells, at first cuboidal, later columnar, with infoldings and plications. In man and fowls, the stage most commonly observed is characterized by an abundance of colloid material—the so-called cystic or colloid goiter of the older writers—while in dogs, sheep, cattle, pigs, fish, etc., the accumulation of colloid is seen only in the late regressive or quiescent stages. In man, the adenomatous form (struma nodosa) is very common, but it is exceedingly rare in all the lower animals. These adenomas, in all probability, arise from fetal cell rests. The stimulus which initiates the growth of the cell rests (adenomas) and that which initiates the growth of the more differentiated thyroid tissue are probably identical. These growths have many of the attributes of tumor, in that their growth may not be arrested by iodin administration or by the natural physiologic compensation.

EXPERIMENTAL PHYSIOLOGY

No accomplishment in preventive medicine has a firmer physiologic and chemical foundation than that underlying goiter prevention, and, as the work of prevention is based on certain of these facts, the more important may be reviewed:

1. The active principle of the thyroid is a very stable organic compound of iodin, first recognized by Baumann, in 1895, and recently (1916) isolated in crystalline form, by Kendall.

2. The developmental stage of all goiters is characterized by an increased blood flow, an increase in the size and number of epithelial cells, a decrease in the stainable colloid, and a marked absolute decrease in the iodin store. The decrease in the iodin store precedes the cellular hypertrophy and hyperplasia.

3. Similar changes (compensatory hyperplasia) invariably occur in the remaining portion of the gland, when a sufficient portion of the entire gland is removed. The amount of gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, definitely, with the age, diet, and the presence or absence of iodin.

4. The administration of exceedingly small amounts of any salt of iodin in any manner completely protects the remaining thyroid against compensatory hyperplasia, even after the removal of three fourths of the normal gland in cats, dogs, rabbits, rats and fowls. Halsted and Hunnicutt reported a series of partial removals in dogs in which they failed to obtain compensatory hyperplasia, while Loeb has recently reported a series of partial removals in guinea-pigs in which iodin failed to prevent the compensatory hyperplasia, although desiccated thyroid still protected. He concluded that regeneration was physiologically different from spontaneous hyperplasia or simple goiter. The explanation for Halsted's results was probably that the animals were in contact with a source of iodin, while the most probable explanation for Loeb's results is that he removed too much thyroid, since, as shown by Marine and Lenhart, in 1909, iodin will not protect even in dogs if more than three fourths of the gland is removed, while desiccated thyroid will protect the animal against thyroid regeneration even after the removal of as much as nine tenths.

5. If most of the thyroid gland is removed before or in the early stages of pregnancy, and rigid precautions are taken to exclude iodin, the young at birth will have enlarged thyroids, as first shown by Halsted in dogs; while, if iodin is available, the young at birth will have normal thyroids.

6. A milligram of iodin, given at weekly intervals, has been found sufficient to prevent thyroid hyperplasia in pups.

7. Thyroid tissue has an extraordinary affinity for iodin, as has been demonstrated in in vitro perfusions of surviving thyroids, and also by injecting intravenously small amounts of some soluble salt of iodin into the intact animal.

8. If the iodin store in the thyroid is maintained above 0.1 per cent., no hyperplastic changes, and therefore no goiter, can develop.

The foregoing experimental data seem to us sufficiently complete to demonstrate the underlying principles of goiter prevention, and the ease with which they may be applied. The first instance in which these facts were utilized in the prevention of goiter on a large scale occurred in 1909 and 1910. Working with endemic goiter in brook trout, Marine and Lenhart were able to demonstrate that iodin added to the water in a concentration not exceeding 1:1,000,000 arrested or prevented the development of thyroid hyperplasia (goiter). Since then, the method has been successfully applied on a large scale by several observers in the prevention of goiter in cattle, sheep, pigs and poultry.

To our knowledge, the prevention of human goiter was not attempted on any large or practical scale until 1917, when we began work with the school population of the city of Akron, although in Cleveland it had been strongly urged and had been used by some physicians for several years. Briefly, the method as applied to man consisted in the administration of 2 gm. of sodium iodid in 0.2 gm. doses, distributed over a period of two weeks,

and repeated each autumn and spring. This amount of iodin is excessive, and far beyond the needs of the individual or of the ability of the thyroid to utilize and store it. One gram distributed over a longer period would be better. The form or mode of administration of iodin is of little consequence. The important thing is that iodin for thyroid effects should be given in exceedingly small amounts, and it is believed that most of the untoward effects recorded are due to the excessive doses employed, or, more concretely, to the abuse of iodin.

The results of our two and one-half years' observations on schoolgirls in Akron are as follows: Of 2,190 pupils taking 2 gm. of sodium iodid twice yearly, only five have developed enlargement of the thyroid; while of 2,305 pupils not taking the prophylactic, 495 have developed thyroid enlargement. Of 1,182 pupils with thyroid enlargement at the first examination who took the prophylactic, 773 thyroids have decreased in size; while of 1,048 pupils with thyroid enlargement at the first examination who did not take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the curative effects. Klinger has recently (1921) reported even more striking curative results in the schoolchildren of the Zürich district. He worked with school populations in which the incidence of goiter varied from 82 to 95 per cent., while our maximum incidence in Akron was 56 per cent. With such a high natural incidence of goiter, his observations necessarily deal more with the curative effects. Thus of 760 children, 90 per cent. were goitrous at the first examination. After fifteen months' treatment with from 10 to 15 mg. of iodin weekly, only 28.3 per cent. were goitrous, of a total of 643 children reexamined.

The foregoing results were obtained in adolescents. There are two other periods in life when simple goiter frequently develops, namely, (1)) in fetal life and (2) during pregnancy. While the thyroid enlargements developing around the age of puberty are more common, they are not more important than those developing during pregnancy and fetal life. The higher birth mortality of infants with congenital goiter is well known. The thyroid enlargement of both mother and fetus may be prevented by giving 2 gm. of sodium iodid, or its equivalent in iodin in any other form, during the first half of pregnancy.

UNTOWARD EFFECTS

The dangers of giving iodin, in the amounts indicated, to children and adolescents are negligible. Exophthalmic goiter and iodism are the two important conditions to be looked for. No case of exophthalmic goiter developed in the series reported by Klinger or by us, although in both instances such cases were carefully looked for. Much has been written of iodin-exophthalmic goiters, but a study of the case reports reveals the fact that they resulted from the use of excessive (according to physiologic standards) amounts of iodin, or of desiccated thyroid. In adults, the possibility of aggravating a mild exophthalmic goiter or even the production of the syndrome in susceptible individuals must be considered. Again, the risk is slight. Iodin should not be given in any frank case of exophthalmic goiter unless the patient can be daily observed, and then it should be administered only in milligram doses. Iodism was observed in eleven cases among the schoolchildren of Akron during the two and one-half years of observation. Most of these cases were very mild, and the girls did not stop the treatment. Klinger did not observe a single instance in sixteen months' observation on more than 1,000 children, although iodism was carefully looked for.

SUMMARY

Simple or endemic goiter in man may be prevented as cheaply and as simply as in the lower animals, by the administration of 3 to 5 mg. of iodin twice weekly, over a period of a month, and repeated twice yearly. Klinger in Switzerland has reported as striking, and nearly as extensive, results as those obtained by us in Akron. In young individuals, with goiter of recent development, the curative effects of exceedingly small amounts of iodin are as marked as one sees in the goiter of animals.

There are no dangers worthy of consideration associated with the administration of the quantities of iodin used by Klinger or by us. Simple or endemic goiter most commonly develops during (1) fetal life, (2) around the age of puberty, and (3) during pregnancy, and we believe that any plan which provides for its control during these three periods of life will practically eliminate endemic goiter. Goiter in the mother and fetus can be prevented as simply as that of adolescence, but, practically, it would seem that it is a responsibility of individual physicians, supplemented by public education. The prevention of goiter of childhood and adolescence should be a public health measure, best administered through the schools in order to combine the important additional factor of education. Beginning with the period of puberty, goiter occurs approximately six times as frequently in females as in males. The question, therefore, whether general prophylaxis should include both males and females would depend to some extent on whether the particular district was mildly or severely goitrous; hence the need for accurate surveys. The age of beginning and stopping the use of iodin would depend to some extent on race and climate. In the United States, probably the maximum of prevention coupled with the minimum of effort would be obtained by giving iodin between the ages of 11 and 17 years.

The prevention of goiter means vastly more than eliminating cervical deformities. It means, in addition, the prevention of those forms of physical and mental degeneration, such as cretinism, mutism and idiocy, which are dependent on thyroid insufficiency. Further, it would prevent the development of thyroid adenomas, which are an integral and essential part of endemic goiter in man, and due to the same stimulus. These multiple, circumscribed benign growths have many of the attributes of tumor, one of which is that their growth once initiated is frequently not controlled by iodin, as are all simple hyperplasias. The terminal metamorphoses are far more serious than those of simple hyperplasia, since, in addition to hemorrhage, necroses, cyst formation, etc., probably 90 per cent. of the malignant tumors of the thyroid arise from these adenomas.

If the prevention of goiter is good preventive medicine, it is better preventive surgery. With so simple, so rational and so cheap a means of prevention at our command, this human scourge, which has taken its toll in misery, suffering and death throughout all ages, can and should be controlled, if not eliminated.