RESULTS OF LONGTERM IODINE PROPHYLAXIS OF ENDEMIC GOITER IN YUGOSLAVIA

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Introduction. Even before the introduction of iodine prophylaxis as a measure of specific primary prevention, a map was made in 1952–1953 on distribution and approximation of the number of cases of endemic goiter in Yugoslavia which was estimated to be over 2 million.

Numerous analyses of water (surface and underground) were made on the territory of the Yugoslav republics and they mostly showed water deficiency in iodine and fluorine. The large number of goiter cases and iodine deficiency in the ecosystem of our population gave base for introduction of general iodine prophylaxis by way of iodized salt, at first with 5 mg of potassium iodide per kg NaCl. From 1954 onwards, the iodine prophylaxis with 10 mg/kg was established in the whole of Yugoslavia. The iodine prophylaxis is regularly carried out now.

On the basis of geological, hydrogeological and epidemiological studies and chemical analyses of water and food, a certain number of places was chosen for investigations, starting from hyperendemic to non-goitrous areas.

Method of work on the control of the iodine prophylaxis effect included, besides goiter testing, anthropometric, endocrinologic, hemogenetic, audiologic, neuropsychiatric, psychologic and stomatologic investigations using modern clinical, biochemical and radio isotopic devices.

Reduction of Goiter. In the village of B. located in a river – flooded plain, in the city of N. P. situated at about 400–500 meters over the sea level and in the mountain village of G. J., on the Jastrebarc mountain – an epicentre of goiter with a high percentage of endemic cretins and deaf-mutes-excellent results were achieved after 14 years of prophylaxis.

The reduction of goiter morbidity is strikingly evident in infants and small children (from 0 to 6 years of age) with rapid disappearance of congenital and nodular forms.

On the basis of the statistical data for 1970 it was found out that the number of simple goiter in Yugoslav school children was irrelevant and the question of goiter in recruits in the Yugoslav army ceased to exist.

Endemic Cretinism and Deaf-mutism. On the basis of epidemiological and clinical studies and statistical data obtained in the area of N. P., the last case of a born cretin
was recorded in 1951. It was evident that the number of so-defectively born children was 5 to 10 cases per year, while in 1960, only 5 years after the introduction of the iodine prophylaxis, this phenomenon was never registered again.

The analysis of the incidence of cretinism and deaf-mutism in the village of G. J. in 1968 showed that 15 years after the introduction of the iodine prophylaxis there were no new cases in children (aged from 0 to 14) with signs of cretinism or deaf-mutism (instead of expected 12 cases).

**Neuropsychiatric Investigations.** There are evident differences between goitrous and non-goitrous cretins such as: non-goitrous cretins have not-enough developed paranasal cavities, longitudinally shortened skull base, short clivus and kyphosis of the base, which shows that the disorder occurred much earlier than in goitrous cretins.

There is a certain difference between the psychic damage and some what less expressed neurologic finding.

There is in goitrous cretins an atrophy of frontal cortex registered by pneumoecephalography.

**Biometric Development of Children.** Growth in sitting height did not follow the accelerated statural development. This is very characteristic for hyperendemic regions during the iodine prophylaxis, for there is a correction of the differential index, i.e., there is a more harmonious development of children in puberty and prepuberty.

**Mental Development of School Children.** This investigation showed that children born during the iodine prophylaxis had better intellectual performance at school than those born before that period.

**Otologic Changes.** On the basis of craniographic changes which are noticeable in endemic cretins, the otologists explain the skull deformation of cretins.

They conclude that platybasia results in narrowing of the tuba auditiva and that deafness and hard-hearing in endemic cretins is mostly of a perceptive type.

**Stomatological Changes.** In the area of the village of B. the stomatologists found out that school children 9 years after the introduction of the iodine prophylaxis, did not show any difference in dentition when compared to children from non-goitrous regions.

**Hemogenetic Factors and Endemic Goiter.** On the basis of hemogenetic investigations we are of the opinion that in our epicentres of endemic goiter and cretinism we do not deal with sporadic genetic cretinism but with cretinism and deaf-mutism caused by iodine deficiency in the ecosystem, independently of blood types. This statement was convincingly proved by the effect of the iodine prophylaxis.

**Isotope Investigation.** It is important to state that the results of 24-hour iodine $^{131}$ uptakes obtained before and at the beginning of the iodine prophylaxis in euthyroid persons from goitrous regions showed values similar to values obtained from hyper-thyroid patients, i.e., they manifested strong avidity for iodine. During further carrying out of the iodine prophylaxis the uptake curve gradually got normal even on hyperendemic regions.

**Pathological-anatomical Changes Appearing during the Iodine Prophylaxis.** Weight reduction of thyroid gland in the first and second decade of life was found to be one of noticeable manifestations of the influence of the iodine prophylaxis.

Pathological and anatomical investigations including 8,195 corpses from four periods
show the percentage of enlarged and altered thyroid glands in the entire corpse material grouped according to age and sex. It is particularly noticeable that the trends of hypertrophy of thyroid gland are on a lower level in the fourth than in previous periods. These data also suggest an encouraging fact: the decrease in frequency of thyroid malignancy.

Conclusion. On the basis of the above mentioned effect of iodine prophylaxis on physical and mental development of children and youths, one can draw the conclusion that the general iodine prophylaxis releases biologic potentials of the population in goitrous areas from the inhibitory and morbid effect of iodine deficiency in the ecosystem and, therefore, enables undisturbed psychophysical development of young generations and in the same time wipes out endemic goiter and cretinism all over the world.
A mass goiter survey, conducted shortly after the War on the whole territory of the CSSR, implied for Slovakia alone the examination of almost 160,000 individuals, i.e., a sample of 4.6 per cent of the total population. These investigations, combined with biochemical studies, disclosed the existence of a highly significant negative correlation between the prevalence of goiter and the iodine content of 24-hour urine, and prompted the Ministry of Health to order the production and distribution of iodinated table salt. Initially, this iodination amounted to 7 mg KI per kg of salt, and concerned only the most affected provinces of Bohemia (since 1947) and Slovakia (since 1951). Later, both territorial coverage and iodide dosage were gradually increased, until finally, since 1965, the prescribed dosage for the whole territory reached 25 mg Potassium iodide per kg salt, with tolerance limits of 15 and 30 mg.

The main reasons for this enhancement of the iodine prophylaxis were the results of various repeated mass screenings in 1962, which showed clearly that the expected beneficial effects were confined mainly to the lower age groups (where a marked and massive decline of goiter prevalence was observed), while the elder adult population exhibited but slight and non-significant changes. Further biochemical investigations had demonstrated clearly, that the values of urinary 24-hour iodine excretion had indeed risen to about twice their pre-iodination levels, but that there remained nevertheless substantial interregional differences. A partial cause of the unsatisfactory effects of the mass prophylaxis were shortcomings of the production and distribution of iodinated salt, which in several instances had failed to meet the prescribed standards.

The question, whether a substantial improvement of the human nutrition during the past two decades in Slovakia did not by itself supply the desirable amount of iodine, was attacked by temporarily suspending the distribution of iodinated salt in two endemic districts as per January 1st, 1967. Each district, a mountainous and lowland endemic one, has some 60,000 inhabitants, and a goiter prevalence of approx. 70 % in adult women. Repeated biochemical and radioiodine examinations of the same subjects from both districts revealed significant decreases of inorganic serum iodine and of urinary iodine excretion after discontinuance of the iodine prophylaxis, while the 6-hour $^{131}$I uptake and the rate coefficient alpha exceeded the upper limit of normal. The PBI levels did not change at all.
We also collected thyroids from suddenly deceased euthyroid subjects from both districts, and also from a third control area. In the first years after the cessation of the iodine prophylaxis, neither thyroid weights, nor thyroid iodine content or concentration differed from the control values. However later, 5 to 6 years after the discontinuance (i.e. in 1971–1972), the averages of both districts under study for iodine content and iodine concentration in the thyroids were lower than in the area with uninterrupted prophylaxis, and tended to decrease even further. The results for the thyroids weights were inconclusive so far.

Our results underline quite unequivocally the importance of a regular iodine prophylaxis for the normal functioning of the human thyroid even under the conditions of an industrialized continental country. All the more so, as an influence of goitrogenic compounds in local foods is likely to be present in several areas.
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THE KANGRA VALLEY EXPERIMENT:
PREVENTION OF HIMALAYAN ENDEMIC GOITRE WITH IODINATED SALT

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The Kangra Valley, located in the Himalayan endemic goitre belt, was selected in 1954 for a prospective study of the effectiveness of potassium iodide and potassium iodate in the control of endemic goitre when added in small physiological doses to domestic salt. The study area was divided into three equal zones, Zone A receiving salt fortified with potassium iodide, Zone C receiving salt fortified with potassium iodate while Zone B served as a control receiving unfortified salt. The levels of iodide and iodate used were such as to supply approximately 200 mcg of iodine per head per day.

The experiment began in 1956 after completion of baseline surveys of goitre prevalence in the three zones which revealed a similar picture in all the three zones. Five to six years later, in 1962 a striking reduction in goitre prevalence was observed in Zones A and C which received salt fortified with potassium iodide and potassium iodate respectively. During the same period, goitre prevalence remained unchanged in the Control Zone B which received plain unfortified salt.

At this point, Zone B, on account of public pressure, had to be abandoned as a negative control and started receiving from 1962 onwards salt fortified with potassium iodate as in Zone C. Zones A and C continued to receive fortified salt as before.

Another six years later, in 1968, systematic surveys of goitre prevalence showed a further reduction in goitre prevalence in Zones A and C and in Zone B, there was substantial reduction from 1962 figures comparable in magnitude to that which occurred in Zones A and C in the first half of the experimental period from 1956 to 1962.

Another 4 years later, in 1972, spot checks by independent physicians in Zones A and B suggested that goitre rates were continuing to decline still further and that in Zone A where goitre prophylaxis started in 1956, children under 10 either had no goitre or negligible amount of it. Radioiodine uptakes and urinary excretion of stable iodide returned to normal limits in areas receiving fortified salt.

It is concluded that endemic goitre can be successfully controlled in the Himalayas by the fortification of domestic salt with either potassium iodide or iodate in small physiological amounts.
FIVE YEARS FOLLOW-UP IN THE TREATMENT OF ENDEMIC GOITER BY IODIZED OIL

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The effects of the treatment and the prevention of endemic goiter by an unique injection of iodized oil has been studied during five years in a very severe goiter endemic in Idjwi island (Republic of Zaire, Africa). The iodized oil used was Lipiodol. The doses injected have been between 125 mg of iodine in new-borns to 1000 mg in children aged 10 years or more, and in adults.

In two villages treated by this method, the prevalence of goiter which was 47% before the treatment, has been drastically reduced to 16% after one year and remained at this level two and a half year later. Five years after the injection the percentage of goitrous subjects is at about half the initial level of prevalence (28%). This evolution of goiter prevalence with time, is critically influenced by the sex of the subjects and the age at which the injection was made. In children the decrease observed after one year, is followed by an increase which is already apparent 3 and a half years after the treatment. In men aged 15 or more and in women aged 40 or more, the treatment brings about virtually complete disappearance of the goiter and this is maintained throughout the five years of observation.

The urinary iodine concentration increased very sharply after the injection and decreases progressively thereafter. Five years after the treatment the mean level of urinary iodine concentration (7.5 mcg/100 ml) is still two to three times the level obtained before treatment. The decrease of the urinary iodine concentration as a function of time is curvilinear. In the first months following the injection, the half live of this concentration can be estimated at about 2 months; it then increases progressively to exceed on average 20 months between the third and fifth years after injection. The 131-I thyroidal uptake at the 24th hour, the thyroxine level in serum and the thyroidal exchangeable iodine pool (Q.G.) has been measured in a group of untreated subjects aged 15 to 29 years and in groups of subjects of the same age treated one and a half years, three and a half years, and five years before. In untreated subjects the thyroidal function is characterized by a very high level of thyroidal uptake (76.0% of dose), together with very low levels of Q.G. (0.62 mg) and serum thyroxine (3.0 mcg/100 ml). The drastic decrease of goiter prevalence which followed the iodized oil injection is accompanied after one year by a similar decrease of thyroidal uptake (37.5% of dose) and by normalisation of both the Q.G. (7.2 mg)
and the serum thyroxine level (6.7 mcg/100 ml). Five years after the injection the thyroidal uptake is still in the normal range (62.5% of dose) and the exchangeable iodine reserves in the thyroid (2.18 mg) are three times larger than before treatment. The normal level of serum thyroxine measured after one year does not undergo any significant modifications during the following four years of observation (5.8 mcg/100 ml at five years interval).

It is concluded that the injection of iodized oil has an effect of a longer duration that it has been generally expected. The observation of a normal serum thyroxine level five years after the injection, suggests the persistence of adequate hormone secretion and thus normal functioning of the thyroid gland at this time interval in adults. In children and young women, however, the reappearance of slight hyper¬trophies of the gland underlines the necessity of a higher periodicity of injections in these age groups using doses identical to the adult doses.

The very great acceptability of this method of treatment for the people concerned, its extreme simplicity and very low cost make it an ideal method for preventing goiter and cretinism in those of the developing countries where large mass campaigns are still the most effective way to treat various endemic diseases.
THE CHAIRMAN'S COMMENT

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This session was devoted to the effect of iodine prophylaxis on goitre incidence or prevalence and on iodine metabolism in endemic goitre areas in Yugoslavia, Czechoslovakia, the Indian Himalayas and in Zaire (Congo). In the three firstly mentioned studies iodine was added to salt as potassium iodide (or in one Himalayan region as iodate) equivalent to 10 or 20 mg/kg. In Zaire the effect of a single injection of iodized oil was studied. The combined evidence indicates that there is no doubt whatsoever about the effectivity of these measures for goitre prevention. A very marked decrease in goitre incidence or prevalence could be observed after 12 to 15 years of iodine prophylaxis by using iodized salt and also a single injection of iodized oil brought about a very marked decrease within one year. The age groups which react most markedly and most rapidly as well to iodine supplementation as to iodine depletion are evidently the very youngest ones. Some relevant points from each of these studies may be mentioned here.

In Yugoslavia (Ramzin et al.) 15 years of iodine prophylaxis (10 mg KI/kg) caused marked decrease in goitre incidence in school children in all regions studied, in a mountainous as well as in non-mountainous areas. The decrease was most marked in those regions with the highest incidence figures. During this period also endemic cretinism and deaf-mutism disappeared entirely. Important was the increased growth potential and improved intellectual ability of the children brought about by the iodine prophylaxis. Other indications of the effect of the prophylaxis was the marked decrease in number of soldiers treated for goitre problems in military hospitals and the significant decrease of the thyroid size of newborns, from 3.15 to 1.8 g.

A similar decrease in goitre prevalence in population studies was seen in Czechoslovakia (Poboda et al.) during a 12-year period of iodine prophylaxis 12 mg KI/kg salt). The most marked changes were seen in subjects less than 20 years of age. During the same period, however, there were also marked changes in the nutritional constituents of the food brought about by the concomitant increasing industrialization. The question arose whether these changes alone could be responsible for the decrease in goitre prevalence. Shortly after introduction of more fortified salt (25 mg KI/kg) a population experiment was designed. Two endemic regions, one in the mountains and one in the Danube valley, which had so far been subjected to iodine prophylaxis were chosen for this study and the supply of iodized salt was prohibited. A third region in which iodine prophylaxis continued served as control area. After one year there was a significant decrease in the urinary excretion of iodine and the plasma
iodide concentration and also in the thyroidal uptake rate. Thyroids from subjects who had died suddenly did not differ, however, in these three regions in their size and the content and concentration of iodine. After 5 years, however, the thyroid size was significantly greater and the iodine content and concentration of the thyroid tissue significantly lower in thyroids from the regions under study as compared to those from the control area. This gives us some idea of the speed by which goitre recurs after abandonment of iodine prophylaxis and is in conformity with some studies in the past as well as with the observations made in Zaire.

In order to study the effect of iodine supplementation purely separated from other factors which possibly may be involved in goitre prevention, three regions in the Indian Himalayas (Sooch et al) which were virtually similar in their goitre prevalence, food habits, nutritional constituents of the food, socioeconomic and climatological factors etc. were chosen for a large population experiment. Iodine was given in amounts equivalent to 20 mg KI/kg salt in one region as KI and in another one as potassium iodate. The third area served as untreated control region. After the lapse of 6 years the goitre prevalence had decreased from the initial value of 38% to less than 20% whereas no change occurred in the control region. After a further 5–6 years the prevalence of goitre was only 9%. In the third region iodine prophylaxis was instituted after the first 6 years period of observation only and after 6 years of prophylaxis the prevalence of goitre had decreased in a similar fashion as in the two other regions during the equivalent period of time. During the time of study also the PBI values increased.

As discussed in another session the administration of iodized oil as injection is an effective measure of goitre prevention. In Zaire on the Idjwi island (Thilly et al.) goitre prevalence and some parameters of iodine metabolism were studied one and up to 5 years after injection. The goitre prevalence decreased rapidly from the initial 47% to only 16% after one year. A marked decrease was seen in all age groups but especially in the very youngest ones. At the same time the originally subnormal serum thyroxine level and the subnormal thyroidal exchangeable iodine pool increased to a normal level. Also the initially markedly elevated serum-TSH concentration decreased profoundly. Five years after the injection the goitre prevalence has increased to 28% and this was particularly due to the recurrence of goitre in the younger age groups. Although at this time the thyroidal exchangeable iodine pool had again decreased markedly, the serum thyroxine and TSH levels remained unchanged in comparison to the values found after one year. Although the urinary excretion of iodine remained slightly low (40–60 mcg/day) the values were still 2 to 3 times those found initially. In this particular area it is thought that some goitrogenic factors are important in the genesis of goitre in addition to iodine deficiency (see other papers in this symposium). Injection of iodized oil seems to overcome the effects of these factors adequately in the initial stage of treatment. It maybe discussed ad what intervals the injections should be repeated for continuous goitre prevention. In adults it seems that 5 years may be adequate but in younger people and especially in young children shorter intervals seem to be important.