insusceptible to infection with polioviruses. The fact that all individuals who were vaccinated with SM virus developed antibody is probably a reflection of the large dose of cytopathogenic virus which was fed to them; the wide range in their antibody titres may indicate the variation in their susceptibility.

Acceptable Attenuated Strains

Although we consider, with our present knowledge, that the TN and SM strains are not at the moment acceptable for mass immunization, this does not mean that suitable strains will not be developed. We have formulated what we believe are the minimum requirements for attenuated poliovirus vaccines. These are as follows:

1. The vaccine virus and any excreted virus should be intracerebrally avirulent for monkeys and perhaps also intraspinally avirulent. Intracerebral avirulence alone may be acceptable provided the other requirements are fulfilled.
2. The virus should not be transmissible from vaccinated to non-vaccinated individuals. This may be difficult to achieve with viruses which are given by mouth and excreted. Sabin (1955a) showed that after intramuscular injection of the KP34 type III strain there was no immunogenic response unless the virus localized in the alimentary tract, where it multiplied and was excreted. This does not mean that strains of poliovirus might not be found which would multiply in tissues other than the alimentary tract but *not* in the C.N.S. Lack of transmissibility is a characteristic of all established attenuated vaccines. Thus 17D yellow fever vaccine is not transmissible by mosquitoes, the spread of vaccinia is rare and limited, B.C.G. does not spread like naturally occurring *Myc. tuberculosis*. If oral vaccines are used, then the duration of faecal excretion of virus should be at such a low level and for such a limited duration (as was claimed for TN virus by Dr. Koprowski) that transmission would be unlikely to occur.
3. The vaccine virus and any of its progeny which are excreted should have some marker which differentiates them from naturally occurring wild strains of virus.
4. The vaccine virus should preferably not multiply in the throat.
5. The vaccine should prevent paralytic poliomyelitis in those who are susceptible. This may not require 100% antibody response in vaccinated individuals.

A live virus vaccine with these properties should be safe to the individual vaccinated and to the community.

Future of Attenuated Poliovirus Vaccines

The future for the types of attenuated viruses developed by Koprowski and by Sabin is not clear. Although Sabin (1955a) states that his KP34 type III strain which he fed to volunteers came out as avirulent as it went in, the KP33 (type I) and KP51 (type II) strains after multiplication in the alimentary tract "yielded a certain proportion of virus particles with increased virulence for brain-stem neurones of monkeys." Sabin indicated that he was continuing his studies to find better attenuated strains. In the evaluation of his published trials, which were done in adults, it should be remembered that the alimentary tract of the small child is probably a better *milieu* for polioviruses than that of the adult.

As already noted, it would seem to us that if strains are found which fulfil laboratory criteria for safety, then they must also be shown to have properties which make them different from wild strains. If these vaccine strains differ from wild strains only in their monkey or chimpanzee pathogenicity, and if they are transmissible, then trials in increasing numbers of people are rendered impracticable because of lack of control. While preliminary trials may be done in institutions, their final evaluation must be in children living in normal environments. There can be no assurance of how the vaccines will behave in a community, for it would seem that mutants of the less virulent naturally occurring strains may occasionally cause paralysis. How else can one explain the sporadic cases of poliomyelitis which occur in communities where extensive inapparent infections are occurring? We have no knowledge of how often mutants arise from naturally occurring avirulent strains, and whether or not they can cause epidemics. No one can

predict what may happen if a community is heavily seeded with a transmissible avirulent virus.

The risks involved in large-scale trials of avirulent poliovirus vaccines may be justifiable in communities where severe epidemics are common. Such trials should only be undertaken step by step, and never without careful laboratory control, however difficult this might be.

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EFFECT OF HYPERMETABOLISM ON THE GOITRE OF A SPORADIC CRETIN

BY

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It is well known that non-toxic nodular goitres may decrease in size as the result of thyroid administration, though to a much less degree than diffuse thyroid enlargements. That this response may be especially evident with hypothyroid nodules was the subject of two of our own recent communications (Zondek *et al.*, 1955; Zondek and Leszynsky, 1956). It was shown that in two siblings with familial sporadic cretinism and large, partly diffuse, and partly nodular goitres the induction and maintenance of a euthyroid state succeeded in one case in considerably reducing the size of the nodules, and in the other in causing the disappearance of four out of five nodules. The diffuse enlargement subsided entirely in both patients.

The purpose of this communication is to show how hypothyroid nodules respond to short-termed overdosage—that is, to the induction of "spurious alimentary hyperthyroidism."

Case Report

The subject of the study was one of the above-mentioned siblings, a girl aged 14. She was first seen at the age of 12. At that time she had, together with the typical features of childhood myxoedema, a large diffuse goitre in which three nodules varying in size between large plums and peaches were embedded. The heart shadow was greatly enlarged (transverse diameter 14 cm.), the B.M.R. was -13% and the blood cholesterol was 310 mg. per 100 ml. Electrocardiography was within normal range. After 1,020 µg. of tri-iodothyronine given within eleven days the clinical picture had in every respect reverted to normal. Both the diffuse and nodular parts of the goitre had at that point greatly decreased in size, and continued doing so during the subsequent four months of maintenance therapy (though irregularly carried out) with tri-iodothyronine and desiccated thyroid. The nodules failed, however, to disappear completely. The patient stopped substitution therapy entirely during the following twelve months.

When she returned to us she was in every respect worse than before treatment: her external appearance and behaviour were even more noticeably myxoedematous, the heart shadow was larger (transverse diameter 15.7 cm.), the electrocardiogram showed definite low voltage and a prolonged Q-T, and the B.M.R. was -25% (oxygen consumption 140 ml. per minute). The blood cholesterol was again 310 mg. per 100 ml. The goitre had increased in size, the neck circumference being 39.5 cm. and the nodules varying in size between a large plum and a goose-egg (Fig. 1). Radio-iodine uptake after two hours was 63%, after twenty-four hours 26%, and after forty-eight hours 14%. These figures indicate that the thyroid was unable to hold and convert iodine into a biologically active protein-bound compound. Radio-iodine excretion was 51% after twenty-four hours and 73% after forty-eight hours. The conversion ratio after twenty-four hours was 30% and serum P.B.I. was 1.8 μ g. per 100 ml.

After receiving 8 mg. of tri-iodothyroacetic acid ("triac") (Pitt-Rivers, 1953) in two days the patient showed prompt overall response. Within the next ten days she lost her puffiness and lethargy, the heart shadow grew progressively smaller, the E.C.G. became normal, the B.M.R. rose to normal values (oxygen consumption 198 ml. per minute = +8%) twelve hours after the first dose, and blood cholesterol fell to around 240 mg. per 100 ml. Since the ninth day oxygen consumption had dropped to 158 ml. per minute. A further 8 mg. of triac administered within two days raised the B.M.R. once more, although less so than after the first dose (gradual rise of oxygen consumption to 177-191 ml. per minute during the subsequent four days). A third dose of 10 mg. of triac had practically no effect at all on the B.M.R. (oxygen consumption remaining at 175-179 ml. per minute). During the period of observation the goitre steadily grew smaller from the second day onwards (Figs. 2-4). As in the first trial with tri-iodothyronine, the diffuse parts responded first, and the nodules somewhat later. After seventeen days the diffuse goitre was no longer palpable (neck circumference 35 cm.), and the nodules had decreased to the size of a small cherry and large olives respectively (Fig. 4).

At that time we tried to make the patient temporarily hyperthyroid (the transient nature of triac activity having already been established) with a view to finding out whether this might lead to complete disappearance of the nodules. For this purpose a total of 30 mg. of triac was given within three days, whereupon the B.M.R. quickly rose to +42% (oxygen consumption 252 ml. per minute) two days after the last dose. Within the following four days the B.M.R. gradually dropped to the baseline. The other indices of thyroid function (external appearance, weight, blood cholesterol, pulse rate, etc.) remained, however, in the euthyroid range during the entire hypermetabolic phase, E.C.G. even showing a partial relapse. There was neither

tremor nor exaggerated sweating. Whereas the diffuse parts of the goitre were still absent, we were surprised to find a steady increase in the size of the nodules, which within six days almost reached their pre-treatment size (Fig. 5). Thereafter, along with a further decrease of oxygen consumption, they again started to regress. A control investigation with radio-iodine at the height of the hypermetabolic phase showed marked hyperactivity over all parts of the gland with regard to iodine collection (55% after twenty-four and 60% after forty-eight hours). Radio-iodine excretion was 35% after twenty-four and 37% after forty-eight hours, and the conversion ratio was 18% after twenty-four hours.

Discussion and Conclusions

It is generally accepted that the ultimate cause of thyroid enlargement, no matter whether of diffuse or of nodular nature, and whatever its primary cause, is to be sought in increased T.S.H. secretion or activity. Conversely, regression of diffuse and nodular goitres alike is ascribed to T.S.H. suppression. The quantitatively different response of diffuse and nodular goitres to T.S.H.-suppressing agents—that is, thyroid substances—indicates that a specific genetic factor should be postulated for the development and regression of thyroid nodules. This factor may probably be ascribed to a focal hypersensitivity of certain areas of thyroid tissue towards growth-stimulating influences (Zondek and Leszynsky, 1956). Circumscribed variations of thyroid function may be ruled out on the strength of isotope studies in this and previously reported observations, no differences having been found in the functional behaviour of diffuse and nodular areas. Neither is it probable that structural differences are of account. It could be shown that excised nodules of this patient and her brother showed uniformly colloid structure.

On the strength of this reasoning it was postulated that the hypersensitivity of the nodular areas towards T.S.H. might best be overcome by raising the levels of circulating thyroid hormone to such an extent as to remove the last vestige of T.S.H. from the circulation—that is, by creating a state of hyperthyroidism. Contrary to our expectations, however, the nodules not only failed to decrease but they even increased greatly in size, thereby indicating that another mechanism which counteracted T.S.H. suppression had come into play. In fact, it became clear that the nodules, in contrast to the diffuse goitre, showed a uniform behaviour with regard to size (Figs. 1 and 5) during the hypothyroid phase and the "alimentary hyperthyroid" phase, which was associated with hypermetabolism and actual, though incomplete, hyperfunction of the thyroid gland. The overall increase of radio-iodine uptake over the thyroid also came as a surprise, it being rather expected that thyroid activity would be entirely suppressed after the ingestion of thyroid substances (see above).

FIG. 1.—A 14-year-old girl with familial sporadic cretinism and goitre, before therapy. B.M.R. -25%. Note the three large nodules within voluminous diffuse goitre. FIG. 2.—Same girl 48 hours after 8 mg. of triac. Note volume decrease of diffuse and nodular goitre. FIG. 3.—Same girl seven days after above therapy. Note further volume decrease of goitre. FIG. 4.—Same girl two days after a second dose of 8 mg. triac. FIG. 5.—Same girl three days after the induction of hypermetabolism through 30 mg. of triac in three days. Note absence of diffuse goitre as contrasted with conspicuous volume increase of nodules.

The paradoxical behaviour of the nodules with regard to size, and of the entire thyroid tissue with respect to function, can in our opinion best be understood in the light of the peripheral theory (Zondek, 1924, 1935), which postulates that primary rise of oxygen consumption in the peripheral tissues may result in secondary hyperfunction of the thyroid, eventually with corresponding increase of its volume. It may therefore be assumed that in our case the artificially induced hypermetabolism led to a secondary stimulation of thyroid function as far as a response of the seriously damaged thyroid tissue could be expected. (Increased formation of an active thyroid hormone was regarded as all the more unlikely, since the B.M.R. subsequently fell.) At the same time only those parts of the gland which exhibited hypersensitivity towards growth-stimulating influences—namely, the nodules—would and did also increase in size. The fact that functional increase was evident throughout the whole thyroid tissue, whereas the increase in size was restricted to the nodules, confirms the claim that function and growth within the thyroid are not necessarily correlated (see above).

It may therefore be assumed that complete regression of thyroid nodules cannot be achieved either in the hypothyroid or in the hyperthyroid respectively hypermetabolic stage, but only if and when a euthyroid state is maintained through adequate and prolonged substitution therapy.

Summary

The case of a 14-year-old girl with familial sporadic cretinism and a very large goitre of partly diffuse and partly nodular nature is reported in which the induction of a euthyroid state resulted in the disappearance of the diffuse goitre and a decrease in the size of the nodules. On the strength of the generally accepted thesis that nodular and diffuse thyroid enlargements are ultimately due to increased T.S.H. secretion and activity, and their regression to T.S.H. suppression, attempts were made to reduce the size of the nodules further by achieving the utmost degree of T.S.H. suppression—that is, by making the patient artificially hyperthyroid. Following the ingestion of large amounts of active thyroid substances (30 mg. of tri-iodothyroacetic acid—"triac"—in three days) a steep but spurious rise of the B.M.R. was obtained, whereas the other indices of thyroid function remained in the euthyroid range. Simultaneously the nodules not only failed to decrease but actually considerably increased in size, almost attaining their pre-treatment volume within six days. Radio-iodine uptake, which before treatment had been very low (with the exception of the two-hour value), rose to abnormally high "hyperthyroid" levels at the height of the hypermetabolic phase; hormone synthesis was not affected.

The unexpected and paradoxical behaviour of the nodules with regard to size and of the entire thyroid tissue with regard to function during the hypermetabolic phase is discussed.

In the light of our observations, regression of thyroid nodules may be expected to take place only in euthyroid conditions, and it must be the aim of treatment to maintain clinical euthyroidism through adequate and prolonged maintenance therapy.

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ATRIAL SEPTAL DEFECT IN THE AGED

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Atrial septal defect accounted for 17% of a series of 200 cases of proved congenital heart disease described by Wood (1950). In his series of cases a sex incidence of 4:1 in favour of the female was encountered and the average age at death was stated to be about 36 years.

Recent advances in anaesthesia and surgical technique (Edwards *et al.*, 1955) have resulted in the inclusion of atrial septal defect among the increasing number of congenital heart lesions now amenable to surgical treatment.

Whilst recognizing the value of surgery in the treatment of a congenital lesion which hitherto has carried such a gloomy prognosis, we feel that this is an opportune time to describe five cases of atrial septal defect in elderly patients which have come to our notice during the past twelve months. All our patients have lived full and active lives, and two of them are still capable of a degree of physical exertion compatible with their advancing years.

Case 1

A widow aged 79 was admitted to the cardiac centre on July 7, 1955, in congestive cardiac failure. She stated that her first episode of cardiac failure had occurred when she was 54 years of age. Prior to that time she had enjoyed good health and was unaware of any cardiac defect. During the last 25 years she had three further attacks of congestive failure, and for the past 10 years dyspnoea on effort had forced her to limit her activities considerably. One month before admission her dyspnoea had increased and was accompanied by swelling of her feet, legs, and abdomen.

On examination she was an alert, intelligent patient who looked younger than her stated age. Slight cyanosis was noted, but she was not anaemic, and there was no finger-clubbing. The pulse rate was 74 a minute, and irregular owing to auricular fibrillation. The brachial blood pressure was 110/80 mm. Hg. The apex beat was difficult to locate and presented as a tumultuous heave extending beyond the midclavicular line. There were no palpable thrills. Marked jugular venous engorgement was noted. On auscultation the abnormalities found were a grade 1 systolic murmur together

FIG. 1.—Case 1. Auricular fibrillation and right bundle-branch block.