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INHERITANCE OF ACQUIRED DIABETES?

Okamoto[1] has reported some fascinating work from Japan, in which he studied the effect of *induced* diabetes mellitus on the offspring over many generations. In the first set of experiments, diabetes was produced in adult rats by means of intraperitoneal alloxan. These rats were mated with diabetic and non-diabetic animals and the islets of their offspring examined after being killed on the 90th day. The number of beta cells was decreased in all offspring when the diabetes in the *father* rat had been present more than 27 days before mating, or in the mother rat more than 24 days. When both parents were diabetic the decrease in beta cells in their offspring was approximately double that seen when only one parent was affected. Similar results were obtained with rabbits and guinea-pigs.

This effect on the beta cells of offspring of alloxan-diabetic fathers was abolished if they had been treated with insulin and rendered aglycosuric for at least 7 days before mating.

In the second set of experiments diabetes was induced in mature rabbits by alloxan, and other means, in rats of the Wistar strain by alloxan and in guinea-pigs by hydrocortisone. The animals were kept diabetic for more than one month and then mated with diabetic or non-diabetic animals. Some of the F1 (1st generation) animals suffering from the same type of diabetes were mated with each other or with non-diabetic F1 animals in order to get F2 animals, after more than one month of diabetes. This process was repeated for several generations and descendants from diabetic ancestors were obtained.

In the islets of Langerhans in these offspring there was evidence of a significant disturbance of beta cell growth, which increased with successive diabetic generations. This disturbance was particularly apparent in mature animals, but it was already seen in the young. Although the average number of beta cells in each islet of Langerhans was 31·4 in normal 120-day-old rabbits, it decreased to 27·2, 22·6 and 16·7 in F1, F2 and F3 offspring of serially diabetic parents, respectively. In F4 animals it was only 13·3, or about one-third of that in controls, and the beta cells were only about two-thirds the size of those in the controls. This same pattern of growth disturbance of beta cells was observed in all types of induced diabetes.

Experiments with Wistar rats and guinea-pigs revealed the same results as in rabbits.

In the pituitary gland a serially increasing change was observed in the distribution of adeno-hypophyseal cells. That is, the acidophiles increased and both the chromophobes and basophiles decreased with successive generations of diabetic rabbits and Wistar rats.

In the adrenal glands of offspring of successive generations of diabetic parents, the zona fasciculata increased in width, and, particularly in F4 rabbits, showed so-called 'massive hyperplasia'.

Next, the minimum dose of alloxan required to induce diabetes gradually decreased from 100 mg./kg. in normal rabbits to 50 - 55 mg./kg. in F4 animals. That of 5-(p-hydroxyphenylazo)-8-hydroxyquinoline diminished from 35 mg./kg. in normal to 20 mg./kg. in F3 animals. In guinea-pigs, the minimum dose of hydrocortisone needed to maintain steroid diabetes for 35 days decreased from 210 mg. in normal to 90 mg. in F3 animals.

An extremely exciting finding was that diabetes developed spontaneously in F4 and F5 rabbits after serial induction of diabetes with alloxan or 5-(p-hydroxyphenylazo)-8-hydroxyquinoline. It occurred approximately 100 - 200 days after birth. However, the severity and duration showed considerable variation.

In Wistar rats, spontaneous diabetes was observed in F5 descendants of diabetic parents and in F7 descendants of diabetic fathers later than 2·5 months after birth. Moreover, F4 guinea-pigs of hydrocortisone-diabetes lineage developed glycosuria spontaneously about 50 days after birth.

Rabbits with spontaneous diabetes were mated to each other after one month's duration of diabetes. When this experiment was repeated through four generations it was found that the incidence of spontaneous diabetes persisting for a long period increased and that it occurred earlier in each generation.

The islet cells from animals with spontaneous diabetes showed hydropic degeneration for 10 days after its onset, and various lesions were seen as the diabetes continued: deterioration, atrophy and marked pyknosis, in addition to hydropic or vascular degeneration. In some islets only one of these was observed, but in others two or three could be seen in various combinations. In some islets, spherically dilated blood-vessels were filled with blood, and in some, large interstices or slight haemorrhages were observed. In one case of not very severe diabetes which had persisted for more than one year, diffuse hyaline degeneration of the islets was impressive.

In 4 cases of 13 long-lasting spontaneous diabetic rabbits, Kimmelstiel-Wilson's glomerulosclerosis was recognized in the kidney.

Experiments on the *recovery* from the diabetic state in further generations can be summarized as follows: The number of beta cells in 120-day-old rabbits averaged 27·2, 22·5, 16·5 and 13·3 per islet in F1, F2, F3 and F4 offspring of serially alloxan diabetic parents. These F1, F2, F3 and F4 rabbits were mated and delivered their young in a non-diabetic state.

The results obtained by this procedure showed, although gradually, an increase in the number of beta cells. It took four generations in F4, three generations in F3, two generations in F2 and one generation in F1 to return to the normal value of beta cell number per islet.

The beta cell number of the offspring from parents, both of which were diabetic, was reduced approximately by 5 from the average number of beta cells of the parents. The beta cell number of the offspring from both non-diabetic parents which were descendants of diabetic parents increased, on the contrary, by 5 from the average number

of beta cells of the parents. There was a further increase of 5 cells in the offspring from the above-described pairs by conceptions under the same non-diabetic condition. In this way the number of beta cells finally returned to the normal value.

The disturbance of the beta cell development in descendant animals is thus not a fixed phenomenon but, as the author says, is unstable.

Okamoto concludes that: (1) Both male and female sex cells are influenced by the abnormal environment, especially on the first and 14th day of the last 23 days of spermatogenesis and of the last 24 days of oogenesis. These influences on the sex cells on two different dates are additively responsible for the growth disturbance of the beta cells in the islets of Langerhans. (2) Even when diabetes has persisted for a long time, if sperm cells or ova are exposed to a non-diabetic environment for at least the last 4 days of their formation, the diabetes does not affect the islets of the offspring. (3) The incidence of spontaneous diabetes in the descendants of spontaneous diabetic rabbits increases and the spontaneous diabetes occurs earlier in each generation. Judged from the histological changes and certain biochemical abnormalities, the spontaneous diabetes induced in these experiments is entirely different from alloxan diabetes, morphologically and physiologically.

These remarkable experiments appear to indicate the inheritance of 'spontaneous' diabetes from an acquired diabetes in the parent. The pregnancy itself is not diabetogenic, since the father is implicated equally with the mother.

It must be concluded that diabetes in *mother or father* has been diabetogenic to the offspring by an entirely unexpected and ill-understood mechanism. If this has any application to man it could invalidate all work on the genetics of diabetes.

1. Okamoto, K. (1965): *Proceedings of the 2nd International Congress on Endocrinology*, Part II, p. 1018. Amsterdam: Excerpta Medica Foundation.

GIFTIGE SLANGE IN SUIDELIKE AFRIKA

Die boek van Fitzsimons oor *Snakes and the Treatment of Snakebite*, wat alreeds in 1919 gepubliseer is, is die laaste boek wat uitsluitlik oor giftige slange en die behandeling van slangbyt in Suidelike Afrika handel, wat gedurende hierdie eeu gepubliseer is. En dié boek is reeds baie jare lank al uit druk uit. Intussen het ons kennis van ons inheemse slange geweldig toegeneem, en sowel noodhulpbehandeling as die behandeling van slangbyt self het groot vooruitgang ondergaan.

Ten einde te voorsien in die lang-gevoelde behoefte aan deskundige dekking van hierdie onderwerp, het die Fakulteit Kaap de Goede Hoop van die Kollege van Algemene Praktisyns mnr. John Visser gevra om die taak van die opstel van 'n geskikte boek te onderneem. Mnr. Visser is in sy eie reg bekend aan museums en universiteite orals oor die land, en ook in die buiteland, deur sy belangstelling in kruipende gediertes van allerlei aard.

Die gevolg van dit alles is die publikasie van die pragboek *Poisonous Snakes of Southern Africa*,[1] wat geskryf is deur mnr. John Visser en geborg is deur die Kollege van Algemene Praktisyns. Die boek is oorsigtelik en betroubaar, en dis opgestel met die doel om in die behoeftes te voorsien van geneeshere sowel as van noodhulporganisasies en lede van die algemene publiek. By sy ander voordele is dit ook nog die eerste gepubliseerde boek wat kleurillustrasies bevat van al die giftige slange in Suidelike Afrika. Hierdie voortreflike illustrasies, waaraan baie tyd en aandag en onkoste gewy is, kan dien as middel tot identifikasie van slange wat by slangbyt betrokke is, en dus ook as waardevolle hulpmiddel by die voorskryf van die regte behandeling.

Die publikasie van dié boek is nie net deur die Kollege van Algemene Praktisyns geborg nie, maar die inhoud daarvan is ook stap vir stap deur die skrywer bespreek met sy kollegas en gekontroleer deur verskeie mediese deskundiges. Dit kan dus beskou word as 'n betroubare bronnegids op hierdie gebied. Die volgende opgawe van die hoofstukke gee 'n idee van die omvang van die boek:

1. Giftige slange van Suidelike Afrika en die uitwerking van hul gif.
2. Faktore wat die ernstigheid van slangbyt bepaal.
3. Teengifstowwe—spesifisiteit, indikasies en voorsorgsmaatreëls.
4. Die behandeling van slangbyt—noodhulp en mediese behandeling.
5. Bylae 1—Noodhulpmetodes
   Bylae 2—Verduidelikende gevalle-inligting
   Bylae 3—Oor slange in die algemeen—vrae en antwoorde.
   Woordelys, Bibliografie, Indeks.

Geneeshere sowel as jeug- en noodhulporganisasies, berg- en toerklubs en lede van die algemene publiek wat in hierdie onderwerp belangstel, word sterk aangeraai om hulself met dié boek bekend te stel.

1. Visser, J. (1966): *Poisonous Snakes of Southern Africa*. Kaapstad: Howard Timmins (R4.50).

ASPIRIN—AN EFFECTIVE THERAPEUTIC DRUG

Correspondence in the *British Medical Journal*[1] has 2 letters emphasizing the usefulness of aspirin in the treatment of pain and pyrexia in children. The first letter points out that it is one of the safest and most useful drugs in use today. Salicylate poisoning can be prevented by educating both parents about the correct dosage and medical students in the dosage and signs of overdosage in children. The second letter emphasizes that there is no effective substitute as an *analgesic*.

Craig *et al.*[2] suggested that aspirin should be withheld from children and that tepid sponging was more effective in reducing temperature—this may be so but the author points out that children should not be made to suffer pain and issues a challenge to try tepid sponging, e.g., in a case of otitis media.

Aspirin is an effective drug, and the concern, almost approaching panic about its dangers, should be allayed by reassurance of the public as to its efficacy.

1. Correspondence (1966): Brit. Med. J., **1**, 918.
2. Craig, J. D., Ferguson, I. C. and Syme, J. (1966): *Ibid.*, **1**, 757.