The frequency of occurrence of diabetic retinopathy has in recent years greatly increased. From a survey made by Oosterbuis (1960) it is clear that diabetic retinopathy can be found in 70% of cases of diabetes of 15 to 20 years standing. The resultant cases of blindness account for between 5 and 13% of the total blindness in the community.

The literature provides us with two groups of data which can be of value in providing us with an understanding of the pathophysiology of diabetic retinopathy. These data are respectively histochemical and biochemical. A recent review of the first type was given by Pope (1960); he has shown that the normal layers of the retinal capillary (the endothelial cell layer, the basal membrane, consisting of 3 PAS-positive layers, and the reticular fibre layer) are all considerably altered in diabetic retinopathy. In his view, the changes begin with a swelling of the endothelial cells, which in the view of Blumenthal, writing in 1959, are interlarded with PAS-positive hyalin fibrils, a change which the latter regards as being specific to diabetes. Subsequently, in Pope’s view lipo-protein deposits are formed between the three layers of the basal membrane, which are thus forced apart. This results in a considerable thickening of the entire capillary wall, with local rupture of the reticular tissue and a risk of local aneurisms, whilst the lumen of the vessel is greatly narrowed.

In the later stages, mucopolysaccharides are also found in these deposits. Another important observation made by Pope was that fat “emboli” are regularly to be found in the narrowed lumina of these retinal capillary.

With regard to the biochemical data, it is seen from Table 1 that investigators are agreed as to the fall in albumin and the rise in $\alpha_2$-globulins, glycoproteins, hexosamines, mucopolysaccharides and $\beta$-lipoproteins; on the other hand there is disagreement as to the changes in total protein, $\alpha_1$, $\beta$- and $\gamma$-globulins, total lipoids, cholesterol and phospholipoids. Very little work has been done on the triglycerides.
Table 1
Survey of various biochemical disturbances in patients with diabetic retinopathy. Those values indicated † are increased, → normal and ↓ lowered.

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Total proteins</th>
<th>Albumin</th>
<th>Globulins</th>
<th>Glyco-proteins</th>
<th>Hexosamine</th>
<th>Lipoproteins</th>
<th>Total lipids</th>
<th>Fatty acids triglycerides</th>
<th>Macroglobulin</th>
<th>Macroglobulins</th>
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Schematic survey of disturbances in the lipoids, proteins and carbohydrates in the blood of patients with diabetic retinopathy and the possible influence of these disturbances on capillaries and retinal tissue.

Influence of diets and medicaments on blood disturbances and retinal tissues in patients with diabetic retinopathy.
and the non-esterified fatty acids, but available evidence points to an increase. The neutral fats in particular are considerably raised.

There thus seems to be a certain parallel between the changes which occur in the retinal vessels in diabetic retinopathy and the concurrent biochemical changes. It is also clear how essential the retinal-capillary system is for the maintenance of retinal function, whilst it is also known that atherosclerosis tends to occur earlier in diabetics than in other individuals. These factors have led to a therapeutic emphasis in recent years on measures to deal with the abnormalities of the diabetic plasma, employing diet or medicaments. A diagrammatic survey of the situation is given in Figures I A and B.

In Figure I A you see the pathological changes in the blood, their influence upon the composition and function of the retinal capillary, and the effect of these latter changes on the retinal tissue. Figure I B illustrates the importance of a combined therapy, basically comprising a rigid limitation on fat intake but with an adequate supply of essential fatty acids, and two different approaches to medication, one aiming at lipoid improvement and prevention of sludging, the other employing anabolic steroids. In addition, attention is drawn to the danger of hypoglycaemia, caused by an excessively rigid insulin regimen (Fig. I A).

Following a favourable report from Valk (1958) regarding his experiences with Durabolin in the treatment of diabetic retinopathy, a group of 107 patients in the Rotterdam Eye Hospital was treated with Durabolin (Nor-androstenolone phenylpropionate) and Deca-Durabolin (Norandrostenolone decanoate). A small group of patients was treated with Orgabolin (ethylestrenol). Ophthalmological examination was carried out by H. E. Henkes and A. L. A. van Poppel. We were able to collect sufficient data to report on 78 patients, of which 65 were women and 13 men. 20 of these were treated with Durabolin, 34 with Deca-Durabolin, and the remaining 24 took part in a double-blind test. I would like to give you here an outline of our biochemical results.

We went to work as follows: The diabetic patients continued to be (insulin-) controlled and periodically examined by their own family doctors and specialists, whilst various ophthalmologists were responsible for the examination and any necessary treatment of the retinal condition. These ophthalmologists referred to us those patients who proved to have diabetic retinopathy, and we carried out on them a thorough biochemical examination every month as shown in Table 2.

We employed doses of 25 mg of Durabolin weekly or 50 mg of Deca-Durabolin every three weeks, both administered intramuscularly. Orgabolin was given in doses of 6 mg daily by mouth.

Our method involved taking a "fasting" blood sample in the morning, the patient having eaten no food since ten o'clock the previous evening. We took all the blood samples ourselves, being careful to avoid such excessive use of a tour-
Table 2
SCHEME OF INVESTIGATIONS IN PATIENTS WITH DIABETIC RETINOPATHY

I. physical examination
   blood pressure - E.C.G. - Organs (Liver)
   vessels (capillary resistance, Rumpel-Leede)
   body-weight check

II. biochemical determinations

A. lipoids
   phospholipoids
   cholesterol (α and β lipoproteins, triglycerides)
   C/P quotient

B. proteins
   normal protein spectrum
   glycoproteins
   lipoproteins
   mucoproteins

C. carbohydrates
   blood sugar
   glucose tolerance
   insulin tolerance
   glycosuria

D. liver function
   bilirubin
   prothrombin time
   thymol turbidity
   alkaline phosphatase

E. kidney function
   concentration test
   urea
   creatinine
   clearance tests
   urine examination

F. serum iron, bindings capacity
   E.S.R. - blood cell picture
   haemoglobin

III. ophthalmological examination (H. E. Henkes)
   electroretinography etc.
   fundus photography (where practicable)
niquet as might alter the water content of the blood, as Koerselman et al. (1961) have recently pointed out. The cholesterol was determined according to the method of Liebermann-Burchhardt and the phospholipoids using molybdoic acid. For the protein spectrum and the glycoproteins we used a modification of Wieme's agar technique (Wieme 1959), which we have described in a publication now in the press; this involves the use of a new colour reaction for the albumin-globulin ratio. We used Burstein's method (Burstein & Samaille 1960) to determine the lipoproteins, Bonte's method, (Bonte 1960) for the mucoproteins, and the Hagedorn-Jenssen technique for serum glucose.

We have reported in detail elsewhere on the ophthalmic results. The general clinical and biochemical results can be classified as subjective or objective. The most striking subjective result was the rapid improvement in the general condition, with a more lively appetite and less tendency to fatigue. Along with this went an increased susceptibility to hypoglycaemia, which proved to be due to reduced insulin requirements. Deca-Durabolin produced in three cases some lowering and hoarseness of the voice, while Durabolin in a very few cases slightly raised the libido.

Increase in weight was only rarely seen, and only a few cases showed loss of weight.

Let me now list the objective results.

Firstly, on Carbohydrate Metabolism.

We regularly observed hypoglycaemias during treatment with Durabolin and Deca-Durabolin; so far we have not found these with Orgabolin. These hypoglycaemias, a result of improved carbohydrate metabolism, were compensated for by reductions in the insulin dosage. They occurred in 20 of the 65 female patients; in other words 31%, and in 6 of the 13 men (or 46%) as seen in Fig. 2.

The reduction in insulin requirement varied between 4 and 56 units, the average being 11.7 units which corresponds to a reduction of 36%. The largest reduction seen was a fall in the daily requirement of Lente insulin from 80 to 24 units. As the insulin requirement fell, there was a decrease in glycosuria. So far as we can trace, no significant changes were made in the diet during this period. Whenever a patient was examined for the first time we carried out a glucose tolerance test; in some of the cases we were able to repeat it 6 months later. Where we did so, we found that a striking improvement in the curve had occurred, as you see in Fig. 3 (Lt).

The insulin requirements of one of our male patients fell during the first three months of Deca-Durabolin therapy from 68 to 24 units of normal insulin, whilst the glucose tolerance during this period was greatly improved (Fig. 3 Rt). Another interesting observation concerned a woman patient with retinopathy who was not known to be a diabetic; the glucose tolerance test however showed a
clearly diabetic picture. The patient was treated with 25 mg of Durabolin weekly, the diet remaining unchanged. The glucose tolerance curve, which we repeated every 4 months, became steadily more normal, as you see in Fig. 4, whilst the fundus signs improved. A final point which struck us was that male patients reacted much better than did females.

I turn now to the changes in Fat Metabolism.

Very shortly after treatment had begun we noticed that in some patients the generally raised cholesterol concentration was tending to fall. This trend continued as subsequent investigations showed. At the same time, a change in the phospholipoids was observed. Since this meant that we would be likely to find a considerable change in the cholesterol/phospholipoid ratio, we proceeded to examine the subsequent behaviour of both the phospholipoids and cholesterol. Three types of reaction - in which the C/P ratio rose, fell or remained stable - were found, as might have been expected by chance selection. But further examination showed us firstly, that the male patients were reacting more strongly, secondly, that as the treatment continued the non-reactive group became progressively smaller, and thirdly that there was a clear correlation between the changes in the cholesterol and in the phospholipoids. I have set out the data in Figs 5 and 6. In
(Lt) Influence of Deca-Durabolin on glucose tolerance in 17 female patients. Glucose tolerance test before treatment and 3 months after treatment.
(Rt) Influence of Deca-Durabolin on glucose tolerance in a male patient. Glucose tolerance test before treatment and 3 months after treatment.

Fig. 4
Influence of Durabolin on glucose tolerance in a woman with a newly discovered diabetic retinopathy; glucose tolerance curves before treatment and 4, 8 and 12 months after treatment (1, 2, 3 and 4 respectively).
Alterations in cholesterol and phospholipoids under the influence of Durabolin and Deca-Durabolin. Classification according to the decrease, unaltered and increased concentration of cholesterol.

Fig. 5

Alterations in cholesterol and phospholipoids under the influence of Durabolin and Deca-Durabolin. Classification according to the decreased, unaltered and increased concentration of phospholipoids.

Fig. 6

Fig. 5 you see the changes in cholesterol alongside the relevant phospholipoid figures. In Fig. 6 just the opposite happened. The fall in cholesterol was found in 23 of the 50 women patients, thus in 46% with a maximum fall from 307 to 244 mg%, a reduction of 17%. Cholesterol was reduced in 8 of the 13 male patients, thus in 62%, the maximum drop being 341 to 240 mg%, a reduction of 30%. In every case, the maximum effect was attained within a few months; this was even the case in those groups where at a later stage the cholesterol was found to be at the original level, or even to have increased.
Influence of sideropenia and renal insufficiency on cholesterol and phospholipoids in patients with diabetic retinopathy being treated with Durabolin or Deca-Durabolin.

The phospholipoids rose quite strongly at first in most groups, this change having a particularly favourable effect on the C/P ratio in the group where cholesterol was reduced.

The effect, again, was much more marked in the male patients.

Since a few of our patients exhibiting the Kimmelstiel-Wilson syndrome continued in spite of this therapy to grow worse, we investigated the possible effect of renal function upon the phospholipoid and cholesterol levels. It transpired that 10 of the female patients (thus 20%) and 3 men (21.5%) had disturbances of renal function. In Fig. 7 you see the cholesterol and phospholipoid reaction in these patients, as well as our attempt to correlate the lipoids with the iron deficiency – a level of less than 60γ% which was present in 13 female and 2 male subjects. This high frequency of sideropenia was not found in other groups, nor among diabetics without retinopathy. It is not yet clear whether there is a causal connection between these two factors.

I will now turn to the question of protein metabolism.

The fact that anabolic steroids are capable of improving an abnormal protein spectrum has already been reported in various publications. It was confirmed once more by the cases we treated. All the patients with diabetic retinopathy
however continued without exception to exhibit lowered albumin and raised $\alpha_2$-globulin fractions. The same disturbance was found in a control group of 25 diabetic patients, though to a lesser extent, as you see in Table 3.

Table 3

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<tr>
<th>No. (sex)</th>
<th>Albumins</th>
<th>Globulins</th>
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<tr>
<td></td>
<td>%</td>
<td>$\alpha_1$</td>
<td>$\alpha_2$</td>
<td>$\beta_1$</td>
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<td>64.4</td>
<td>4.3</td>
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<td>53.1</td>
<td>6.0</td>
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<td>50.1</td>
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<tr>
<td>Diabetics with retinopathy after treatment</td>
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<td>59.5</td>
<td>3.7</td>
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<td>60.5</td>
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N.B. Figures obtained by agar electrophoresis without correction factor.

During the treatment with anabolic steroids a large proportion of patients showed improvement in the protein spectrum. The total protein level was reduced in only 4 patients; these four were all losing a great deal of protein in the urine. The blood protein level of these patients rose during treatment with anabolic steroids from an average of 56 to 72 grams per litre, usually with a concurrent reduction in oedema and fall in the blood urea. In 35 women (thus in 69%) the albumin level rose from an average of 50.1% to 59.5, in another 13 women (thus in 26%) it fell from 56.5 to 49.9%, as seen in Fig. 8a. Only 2 female patients failed to show any change in the protein spectrum during treatment. As the albumin content improved so the $\alpha_2$-globulin - and to an even more marked degree the $\beta_1$-globulin fell, whilst in patients whose albumin concentration deteriorated the $\alpha_2$- and $\gamma$-globulin rose. Of the 13 male patients, 11 showed improvement in the protein spectrum (Fig. 8b).
As to the glycoproteins, we investigated possible changes in 30 female and 8 male patients with diabetic retinopathy. 18 women exhibited a lowering of the $\alpha_2$ glycoprotein concentration, 2 showed no change, and in 10 the $\alpha_2$ glycoprotein rose after one year's treatment. Of the patients showing improvement in the lipoids 72% exhibited a fall in the $\alpha_2$ glycoproteins, which was similarly regarded as an improvement. Of the 10 women with rising glycoprotein levels 9 showed a concurrent rise in cholesterol, which suggests that there is some con-
nection between fat metabolism and glycoprotein synthesis. Among the 8 male patients we in one case observed a rise in the $\alpha_2$ glycoprotein concentration. This was the same patient who had shown a deterioration in the lipoids. All the other patients showed a fall in the $\alpha_2$ glycoprotein concentration.

Since so little was known as to the psychosomatic effect on the diabetic metabolism of a treatment perhaps capable of preventing blindness - a conscious threat to many retinopathy sufferers - we carried out a double-blind test on 26 successive patients. Half of this group received Deca-Durabolin, the other simply the vehicle (an oil). As it happened, we had in each treatment group 12 women and 1 man. 2 women unfortunately did not complete the trial; both belonged to the group which later proved to have been the Deca-Durabolin group.

The average age of the placebo group was 63.2 years, that of the control group 58.7 years; the average insulin requirement was 24 and 30 units daily respectively, the average blood pressure 195/100 as against 190/100, the two groups thus differed little from each other in these respects.

![Influence of placebo-substitution on Cholesterol and Phospholipids](image)

**Fig. 9**
Influence of placebo and Deca-Durabolin on cholesterol and phospholipoids in patients with diabetic retinopathy.

To our surprise both these groups showed a reduction in blood cholesterol (Fig. 9). After six months treatment, this fell in the placebo group from 287 to 252 mg%, and in the Deca-Durabolin control group from 273 to 225 mg%. This represents an equally significant fall in each group. The main difference lay in the cholesterol decrease during the first two months; the Deca-Durabolin group showed a characteristically fast decrease, whereas the placebo group had not at that stage fallen significantly. The phospholipoids did not change appreciable in either of the two groups.

A more marked difference was seen in the changes in blood proteins. In the placebo group two improvements were recorded, two unchanged spectra, and the
remainder showed a deterioration. In the Deca-Durabolin group there was a deterioration of the protein spectrum in 2 cases; whilst in all the others the protein spectrum improved, the albumin rising from an average of 54.9 to 59.3% and the α₂ falling from 15.1 to 10.3%.

As regards the carbohydrate metabolism, a marked decline in insulin requirements was seen in 4 patients in the Deca-Durabolin group but in only 2 of the 13 cases receiving placebo (if one includes male patients). In one of these latter placebo patients the insulin was reduced from 56 to 22 units daily, without her becoming uncontrolled. The male placebo patient did not react.

From these provisional data it is clear that psychic factors can play an important rôle. It is probably true, as Schwarz (personal communication) has suggested that, along with the new treatment, some patients begin to follow their diet and other aspects of their diabetic regimen more strictly. So far it has not been possible to track down precisely these factors in the patients concerned.

What now of the patient’s vision? In order to be as objective as possible in gathering data, the biochemical and ophthalmoscopic examinations were carried out separately, and later compared. Since the patients had come from various ophthalmologists we based our initial conclusions exclusively on the data recorded at examination in the Eye Hospital since all cases had been examined there by the same person. (Dr van Poppel). There were in all records concerning 78 eyes, 12 of which belonged to the placebo group. One difficulty arose from the fact that in some patients one eye could not be recorded, whilst here and there were cases where the two eyes of a single patient reacted differently. For that reason we decided to base our conclusions on the total number of eyes each considered as a separate entity, and only subsequently to go into the question as to whether in patients showing marked changes there was any association between the conditions in the left and the right eye. The eyes were classified according to the cholesterol reaction, an effort being made to identify any link between the improvement, stability or worsening of the cholesterol concentration and the changes in visus and fundus. We have already gone into this question in detail elsewhere (Henkes et al. 1961).

There indeed seems to be a connection between the changes in the serum constituents and the alterations in the visus and fundus, as you will see in Fig. 10. This was particularly the case as regards the fundus picture, which can be more objectively assessed. In the group showing biochemical improvement we found the highest number of cases with an improved or unchanged fundus; on the other hand, in the group showing a biochemically poor reaction, there were no fundal improvements and the highest number of deteriorations.

During the treatment with anabolic steroids vision remained unchanged or improved in 74.5% of the cases, the fundus in 60%. There was deterioration of the
Correlation between biochemical alterations (cholesterol) and eye disorders (vision and fundus) in 66 patients with diabetic retinopathy during treatment with Deca-Durabolin and Durabolin.

vision in 7.5%, of the fundus in 18%. The ophthalmic improvement was greater than we at first expected, particularly since most of the patients already had an extensive retinopathy. The cases with mild retinopathy proved to react better than the serious ones, which would seem to confirm the correctness of the therapeutic principles which I showed you in Fig. I B.

May I return to Fig. 1 A. I have shown you some of the biochemical improvements which we found in the lipoid-, protein- and also in the carbohydrate metabolism of the patients with diabetic retinopathy who were treated with these anabolic steroids. As is evident from Fig. 1 A these three groups of metabolic improvements have a favourable influence on the capillary wall and especially on the retinal tissue. We feel that for the moment we are on the right track, but of course we are still awaiting the final results of our studies. However I think that we shall have to go further perhaps two or more years before we can be absolutely certain of the value of these steroids.

I hope that there will be other clinics, not only ophthalmological ones, which will carry out the same kind of investigations as we have done. And I hope that investigations will not only be limited to cases with severe retinopathy, such as those with which we had to deal, but also that the effect of anabolic steroids will
be studied in those cases without retinopathy or with very mild forms. It is in these latter cases that we have most chance of improvement. May I end by expressing to Prof. Tausk and the rest of his staff my gratitude for the help which they have given to our clinic and without which it would not have been possible to have carried out these investigations.

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DISCUSSION

Tausk: Thank you very much Dr Houtsmuller for this very comprehensive report on the enormous amount of work and of data you have collected.

Prader: I am most impressed by both papers. The hypoglycemic effect of these
steroids is quite extraordinary. I did not understand exactly whether you saw this
effect only after Durabolin treatment or after treatment with other anabolic ste-
roids as well? That is my first question. The second question is from a pediatric
point of view. I am astonished at the insulin-sparing effect of anabolic steroids
because diabetes mellitus usually gets worse during puberty when the endogenous
production of anabolic steroids increases. Is it not paradoxical that anabolic steroids
should improve diabetes and that puberty should make it worse? Also I am won-
dering whether you have any experience with these steroids in diabetic children and
whether anabolic steroids can be given prophylactically to prevent diabetic retino-
pathy?

Dardenne: I believe the effect on hyperglycaemia may be dose-dependent and I think
that the reason that I have not seen such strong effects as Dr Houtmuller is because
I used lower dosages. No effect was seen of ethylestrenol on the bloodsugar. There
was a temporary rise in sugar excretion which vanished again. Formerly I used me-
thyltestosterone and did not see any effect on the bloodsugar but the doses em-
ployed were not very high. As to the second question of sex-distribution and age-
distribution in diabetic retinopathy: we saw it at every age, 20, 40 and 60 years.
The incidence in male patients accumulates between 16 and 20 years and increases
again towards the end of life. In females there is a steep rise after the climacterium.

Houtmuller: We did not examine all anabolic steroids but we know from our col-
legues in Rotterdam that methandienone also has a hypoglycaemic action. I know of
three cases with a lowering of insulin requirement after giving this substance.
Neither did we see, as Dr Dardenne did, any case with hypoglycaemia after giving
ethylestrenol. We now have 10 patients treated for four months with ethylestrenol,
and they have had a remarkable decrease of cholesterol and also a change of the
phospholipoid concentrations. We dare not say too much about this as we first have
to see a much larger group. Also the course of the cholesterol values in the placebo
groups has to be taken into consideration - particularly when, if I understood
Dr Overbeek correctly - it is hardly likely that effects on the cholesterol and phos-
pholipoids could be anabolic or androgenic ones. As I understand you, there is
hardly a hypocholesteremic action possible with these hormones. We also have to
conclude that there are secondary ways present, psychosomatic perhaps or other
conditions for the improvement of fat-metabolism. Nevertheless there is an
improvement in diabetic retinopathy and I think this is very important.

Bierich: We have no personal experience of using these steroids in this disease but
I have heard of one or two other clinics having similar results - that is an improve-
ment following the administration of anabolic steroids. Now it is most surprising to
hear that anabolic steroids have such an effect on glycaemia and on sugar tolerance
whereas we know that growth hormone induces the contrary, the glucose tolerance
deteriorates. Therefore the question is whether or not you believe it to be possible that these patients have insulin in reserve and that their own insulin producing capacity is raised by giving anabolic steroids comparable to the action of certain sulphanylureas.

Houtsmuller: I think it is possible that there is a general improvement and therefore also an improvement in pancreatic function. There is however another possibility. Hollmann (Nicht-glykolytische Stoffwechselwege der Glukose, Stuttgart (1961) 66) mentioned that a combination of oestrogens and androgens gives an improvement of some enzymatic reactions of the pentose phosphate shunt, whilst the glucose-6-phosphate dehydrogenase inhibitor glucosamine-phosphate decreases. Perhaps that would be a reason for the improvement of the carbohydrate tolerance, however these kinds of studies are still continuing.

Bierich: Are not these patients mostly juveniles? The beginning of diabetes in these cases is very early. There are two types, the juvenile asthenic diabetes and the sthenic one of adults. In most of your patients diabetes probably began in youth.

Dardenne: It has often been observed that patients with a very unstable bloodsugar and high bloodsugar fluctuations stabilize as soon as they get retinopathy. Patients who have a high excretion of acetone- and ketone-bodies in the urine have a reduced tendency to develop retinopathy. There are a lot of theories on the influence of protein-sparing anabolic hormones on diabetic retinopathy. It is not known whether there is any influence on insulin production. As far as the influence on enzymes is concerned we do not know whether there is an influence on enzyme activity or on enzyme production. Maybe there is a disturbance of carbohydrate metabolism so that less carbohydrate is utilized for fat synthesis and more intermediates of carbohydrate metabolism are available for protein syntheses.

Houtsmuller: We generally have very old patients. We have not seen any children. It would be very interesting to study this disease in children because they do not yet have the complication of atherosclerosis.

Bierich: We have not seen retinopathy in our diabetic children under the age of 13.

Dardenne: Retinopathy in children greatly differs from retinopathy in adults. There are morphological and histological differences. Children have a very strong tendency towards the new formation of capillaries and these infantile forms of retinopathy have not responded to Durabolin treatment.

IJzerman: I would like to come back to the hypoglycaemia. Do you think it is possible that this is linked also with the antcatabolic effect? It is well-known that the corticosteroids cause gluconeogenesis and it is quite possible that the antcatabolic effect (whatever that may be) is responsible for the hypoglycaemic effect. Since Dr Dardenne has pointed out that this is so dose-dependent and as Dr Houtsmuller has stated that he only gets the effect with very high doses of Deca-Durabolin, it would be of interest to know the doses which have been used in other cases.
for example in those cases treated with ethylestrenol and methandienone. We know that doses of androgens which may cause this effect have to be very high as well.

Dardenne: I believe that the favourable effect of anabolic steroids on diabetic retinopathy may well have to do with the anticalcobic effect of these steroids but I do not believe that the hypoglycaemic effects can be entirely explained by this anticalcobic effect. I also think that Kochakian’s observations point in the same direction. With ethylestrenol, at a dosage of 4 tablets of 1 mg per day we have not until now seen any influence on the bloodsugar.

Houtsmuller: This reminds me that I have forgotten to mention the dosages. We used 25 mg of Durabolin per week, 50 mg of Deca-Durabolin per three weeks and 6 mg of ethylestrenol per day. My colleagues in Rotterdam are using 5 - 15 mg methandienone per day.

Overbeek: I do not understand at all why the hypoglycaemic effect occurs. Some suggestions have been made: the anticalcobic effect, insulin-production and so on, but I think it is pretty improbable that this is the case. First of all because you showed that in normal pubers the endogenous androgens have no effect whatsoever. In normal animals we have never observed any effect on bloodsugar or on insulin sensitivity and in contradistinction to the observations of Kochakian, we have never seen any effect on the insulin sensitivity of pancreatectomized dogs. If it is a matter of production of insulin by the pancreas then why has no effect been observed in normal animals or in normal men? And if it is an anticalcobic effect why is nothing seen at all? It also struck me that the effect occurs - at least in Dr Houtsmuller’s experiments - in about 25% of the treated cases. I wonder why the other patients do not respond and why you do not see any effect on other subjects apart from those with diabetes?

Tausk: May I add one remark for your consideration? Is it not the case that the normal organism has so many means of regulation and counter-regulation that many effects, particularly on these metabolic phenomena, might not become visible whereas in diseased persons these counter-regulations are either missing or not operating.

IJzerman: Corticoids do not in general influence the glucose tolerance curves, but they do in diabetics.

Deggelmann: Dr Prader has asked about the prophylactic use of anabolics which I believe is a particularly important matter. I should like to know whether such use is advisable and if so how should it be done?

Dardenne: We are trying in our department to perform such prophylactic treatments with insulin and with low doses of anabolic steroids. I have been thinking of treating them for a three month period.

Hoet: May I ask Dr Overbeek one question? Did you ever see an increase in the
glycogen contents of the liver when you were giving Durabolin or Deca-Durabolin, either to normal animals or to adrenalectomized ones?

Overbeek: Never.

Hoet: Of course it is always quite impressive to hear about the progress done in the prevention of degenerative diseases and it is stimulating work to find the ways and means of arresting the degenerative lesions provoked by diabetes. If I understood correctly there was first an effect on the fundi of the eye in both your series. Was it in about 50 - 60% of your patients that you definitely saw an improvement?

Houtsmuller: The improvement and the standstill. The improvement is very little, about 16 - 17%. The standstill of the symptoms is much greater but we have material which is very, very bad to work with.

Hoet: So, you have a standstill and a follow-up of how many months?

Houtsmuller: The patients treated for the longest period have now been treated for two years.

Dardenne: We have treated them with Durabolin for 1 1/2 years but we have also patients treated with testosterone-propionate for 4 - 5 years, in which no progress of the disease was seen.

Hoet: How long is your follow-up in the 16 - 17% of your cases in which you saw an improvement?

Houtsmuller: 9 months.

Hoet: I am quite impressed with the effect on the bloodsugar. I should very much like to know what type of reactions the patients have with regard to their bloodsugar? I am thinking here especially of what one may see with sulphanylamides. There is at first a decrease of the bloodsugar and a decrease of the insulin requirements. Four or six months later there might be an increase in their insulin requirements which may rise to higher levels than before. I would like very much to know if you have had any experience of that sort.

Dardenne: I have never seen that the insulin requirement went up again during treatment. I am no longer giving the high doses that I used to give and I am now giving more normal doses of about 50 mg of Deca-Durabolin every three weeks. I also think it is important to consider the type of patients because I have had patients who showed no effect on bloodsugar with very high doses of Durabolin. Until now we have not had enough patients to make a differentiation according to the type of reaction which would enable us to say which patient will react with a lowering of the bloodsugar and which will not.

Houtsmuller: We have seen two patients who after about 7 months have a slightly increased need of insulin. Both were women of the small meagre asthenic type.

Tausk: Gentlemen, we have to think of our time and in fairness to two more speakers who are on the schedule, we must somehow shorten this discussion although it is extremely interesting.
Hoet: Did you check the acetonaemia in patients and was there a decrease in the acetone bodies in the blood or of the acetone in the urine?

Houtsmuller: I did not measure acetone in the blood but in the urine they were gradually stabilized.

Pateisky: Were there any neurological complications?

Houtsmuller: Yes. I did not talk much about this because they are a large group of symptoms. We never saw any improvement in neurological complications.

Tausk: Thank you very much. I am sorry we have to close this discussion.