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THE HORMONAL PRODUCTION OF NEPHROSCLEROSIS AND PERIARTERITIS NODOSA IN THE PRIMATE

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[WITH SPECIAL PLATE]

Most of the experimental work on the possible participation of the adrenal cortex in the production of renal and cardiovascular lesions has been performed on the rat, because this species is especially sensitive to deoxycorticosterone, the most readily available mineralocorticoid. It had been clearly shown that overdosage with deoxycorticosterone can produce nephrosclerosis in rats, but many investigators considered it unwarranted to assume that, therefore, endogenous mineralocorticoids might participate in the pathogenesis of similar diseases in man. It was pointed out that rodents may occasionally develop periarteritis nodosa spontaneously and that the corticoid metabolism of the rat is fundamentally different in many respects from that of primates. (For literature see Selye, 1950, 1951; Selye and Horava, 1952, 1953; Selye and Heuser, 1954, 1955-6.)

In answer to these objections we attempted many years ago to produce renal and cardiovascular changes with deoxycorticosterone in rhesus monkeys, but found that even the highest tolerated doses of this steroid produced no periarteritis and only moderate degrees of nephrosclerosis in occasional animals. Besides, the renal lesions which occurred were invariably accompanied by often fatal spells of hypokalaemic paralysis. This high mortality precluded long-term experimentation and, in any event, clinical nephrosclerosis is not usually accompanied by muscular paralysis, so the experimental syndrome produced with deoxycorticosterone did not truly duplicate the disease as it occurs in man (Selye and Hall, 1943). Subsequently we learned that, in primary aldosteronism, nephrosclerosis and hypokalaemic paralysis do occur conjointly in patients (Conn and Louis, 1955-6), but this merely strengthened the view that if the disease produced by deoxycorticosterone in the monkey had a clinical counterpart it would be primary aldosteronism and not ordinary nephrosclerosis or periarteritis nodosa.

The recent discovery that the introduction of a methyl group at C² greatly enhances mineralocorticoid activity in certain steroids (presumably because it interferes with their normal metabolic destruction and activity) furnishes us with new tools with which to study this problem. It was found that 2-methyl-9(α)-fluorocortisol and 2-methyl-9(α)-chlorocortisol are more effective by far than aldosterone in producing sodium retention and

potassium excretion (Byrnes *et al.*, 1956) as well as in inducing nephrosclerosis and periarteritis nodosa (Selye and Bois, 1956 a-d) in the rat. In fact these two methylated compounds are the most active mineralocorticoids discovered up to now. It seemed to be of interest, therefore, to establish their toxicity in a primate before introducing them into general practice. We also hoped that such experiments would give us further indications concerning the possibility of reproducing nephrosclerosis, and perhaps even periarteritis nodosa, with comparatively small doses of a steroid, and that in an animal more closely related to man than is the rat. Of course, the success of such an experiment would depend upon the ability of 2-methyl-9-halo-corticoids to produce morphologic changes at dose levels that do not cause fatal paralysis. We hoped that this might be possible, as both these steroids possess some degree of glucocorticoid activity, in addition to their extraordinarily pronounced mineralocorticoid effects. These two activities of steroids are antagonistic in most respects (inflammation, lympholysis, catabolism), but synergistic as regards the production of renal damage.

In the present communication we wish to present data which show that, in fact, 2-methyl-9(α)-fluorocortisol (Me-F-COL) can produce marked nephrosclerosis and periarteritis nodosa in the rhesus monkey without causing muscular paralysis.

Materials and Methods

Eight young female *Macacus rhesus* monkeys, having an initial body-weight range of 1.8-2.7 kg., were divided into three groups whose mean initial body weight varied between 2 and 2.4 kg. On the first day of the experiment the right kidney was removed under sterile conditions through a sub-costal incision in all animals to sensitize them for the possible nephrotoxic actions of Me-F-COL. For the same reason a 1% NaCl solution was supplied as the sole source of drinking fluid, but the animals did not take much of this solution and tried to get their fluid mainly from the abundant amounts of vegetables (carrots, cabbage) and fruit (oranges, lemons) which were made available to them, together with a ground wheat and soy-bean meal diet as a source of nourishment.* Group I (two animals) was other-

*The basic diet was kindly adjusted with vitamin and mineral supplements by Dr. P. Marois as based on his experience with the feeding of the large monkey colony of the Institute of Microbiology of the University of Montreal.

wise untreated. In Group III (two animals) both adrenals and the right kidney were removed simultaneously through subcostal incisions. These adrenalectomized monkeys, as well as those of Group II (four animals), received Me-F-COL in the form of microcrystals in aqueous suspension, subcutaneously. The drug was administered daily in a single injection: 1 mg. in 0.5 ml. during the first week, 2 mg. in 1 ml. during the second week, 4 mg. in 1 ml. during the third week, 8 mg. in 0.5 ml. during the subsequent four days, 16 mg. in 0.5 ml. during the next ten days, and then 8 mg. in 0.5 ml. until termination of the experiment on the 80th day.

All animals recovered from the operations without complications, but soon the adrenalectomized monkeys of Group III became obviously ill, refused to take food, and exhibited signs of great weakness, especially in the muscles of the neck. This was thought to be due to hypokalaemic paralysis such as we had previously seen in monkeys overdosed with deoxycorticosterone (Selye and Hall, 1943). The animals were consequently given repeated intravenous injections of 1%–3% KCl solutions. They seemed to rally after each injection, but relapses continued, and, despite treatment with Me-F-COL, both the adrenalectomized animals died, one on the tenth, the other on the eleventh day after the operation. The remaining six monkeys were killed, under pentobarbitone sodium anaesthesia, by exsanguination on the 80th day, and their organs were removed and fixed in Susa solution for subsequent weighing and histological study.

Results

We shall discuss our observations on the two adrenalectomized monkeys first, because, as these animals died within the first fortnight, the results obtained were not comparable to findings in the other six monkeys, with which this communication is chiefly concerned. As explained in the preceding section, recovery immediately after adrenalectomy was uneventful, but in the course of the next few days repeated attacks of great muscular weakness developed in both animals, and intravenous administration of KCl was only partially successful in relieving these spells. Curiously, histological examination of the tissues in both these animals revealed an almost leukaemia-like infiltration of the hepatic stroma with mature and immature white blood cells; in many blood vessels (especially in those of the renal medulla and liver) there was a striking predominance of polymorphonuclear leucocytes in various stages of maturation. In the blood of the vessels we also found a great deal of strongly basophilic, amorphous material somewhat reminiscent of the so-called "haematoxylin bodies" of Klempner. At the same time oedema of the adventitia developed, sometimes accompanied by hyaline necrosis of the subintimal layers, in many arteries throughout the body. There was also some oedema and thickening of the endocardium with patches of hyaline necrosis. It was tempting to attribute this whole syndrome to some accidental infection, but the operations were performed under strict aseptic conditions, and, for the sake of greater security, 50 mg. of chloramphenicol was administered intramuscularly to all eight monkeys, both on the day of the operation and 24 hours later. Besides, no sign of infection was visible in any of the non-adrenalectomized animals. It is also unlikely that the syndrome could have resulted from mere adrenal insufficiency, since KCl did not aggravate it and treatment with the highly potent Me-F-COL had been initiated several hours before surgical intervention. Although neither of these possibilities can be excluded with certainty, it seems more probable that the adrenalectomized monkeys—notoriously sensitive to corticoid overdosage—merely exhibited a particularly acute syndrome of Me-F-COL intoxication. We intend to perform systematic studies on the response of adrenalectomized monkeys to 2-methyl-halo-corticoids as soon as these compounds become more readily available, so here it will suffice merely to mention these unexpected reactions.

Organ Changes in Treated Animals

The organ changes in the four non-adrenalectomized Me-F-COL-treated animals, which form the basis of this report, were essentially the same in all individuals and may therefore be discussed conjointly.

During the period of observation the untreated controls showed a mean gain corresponding to 12% of their initial body weight, while the monkeys treated with Me-F-COL lost 5% of their initial weight. Two of the monkeys in this latter group developed a moderate puffiness around the eyes and some bluish cutaneous striae around the abdomen.

At necropsy it was noted that all but one of the Me-F-COL-treated monkeys had abundant stores of adipose tissue underneath the skin of the abdomen and in the mesentery, despite the over-all loss of weight. In three of the treated animals chalky yellow patches of steatonecrosis were seen in the fat throughout the omentum and mesentery. In these foci histological examination revealed the presence of many foreign-body giant cells with needle-shaped intracellular spaces, which apparently corresponded to dissolved fatty acid crystals.

The most striking macroscopic changes occurred in the kidneys. These were definitely enlarged in all the treated animals (9.9–11.9 g.), as compared with the controls (6.3–6.7 g.). The renal surface was pale and mottled with numerous punctate light-grey or red spots. The outstanding characteristics of the renal lesions are illustrated in the Special Plate, Figs. 1–4. The minute red spots which were macroscopically visible on the surface of the kidney corresponded to focal glomerular haemorrhages. Many of the glomeruli were partially hyalinized, and on sections stained with the PAS technique the thickening of the basement membranes around Bowman's capsules and the proliferation of the glomerular stroma with "intercapillary glomerulosclerosis" were particularly evident. Some of the glomerular capillaries showed the "wire-loop" appearance due to accumulation of PAS-positive hyaline material underneath the endothelium. Often this progressed so far that large, pearl-like accumulations of hyaline material took the place of glomerular loops, and a picture indistinguishable from the renal manifestations of the Kimmelstiel-Wilson syndrome resulted. Many of the afferent glomerular arterioles underwent hyaline necrosis and numerous tubules were obliterated with hyaline casts. In a few areas the stroma of the kidney was infiltrated with leucocytes and showed some sclerosis; the stroma of the renal pelvis and papilla was oedematous in all the treated monkeys. None of the control animals showed any abnormality in renal structure.

The heart was manifestly enlarged (11.2–16.8 g.) as compared with the controls (10.2–10.5 g.), and even mere macroscopic inspection immediately revealed the presence of pronounced periarteritis nodosa in the coronary vessels of all four Me-F-COL-treated animals. The lesions were particularly pronounced along the anterior descending branch of the left coronary artery, which assumed a rosary-like aspect due to the inflammatory nodules. Histological examination showed that most of the branches of the coronary arterial system were affected. In some instances the periarteritic changes extended to all parts of the arterial wall and led to considerable hyaline necrosis, especially in the media and the subintimal layers. Occasionally the endothelium was totally destroyed, and thrombus formation occurred on the denuded surface. However, the aspect of the arterial lesions was quite polymorph, and within the same heart it was possible to find acute necrotizing and thrombotic arterial lesions as well as largely organized obliterative endangitis in different branches (Plate, Figs. 5–7).

The peripheral vessels were not systematically examined in all organs, but definite periarteritic lesions have also been noted in the gall-bladder, pancreas, kidney, and urinary bladder. Although the intensity of the lesions differed from case to case, all four Me-F-COL-treated monkeys exhibited signs of advanced periarteritis nodosa.

The arterial blood pressure had to be taken under profound pentobarbitone sodium anaesthesia by the direct intra-arterial (femoral artery) method, and therefore gave values which were probably much below the normal resting blood pressure. Yet it is noteworthy that, under identical conditions, the mean blood pressure in the controls was 62 mm. Hg (60–65 mm. Hg), as compared with 110 mm. Hg (75–135 mm. Hg) in the Me-F-COL-treated monkeys. These observations, as well as the already mentioned great cardiac hypertrophy, imply that the steroid did produce an elevation of blood pressure.

In the pancreas the most conspicuous changes were observed in the islets of Langerhans. In three of the four Me-F-COL-treated monkeys many of the islets (and in one animal almost all of them) contained cystic cavities filled with a poorly tingible homogeneous fluid. Some of the islets were almost totally transformed into cystic spaces. There was also a conspicuous hypertrophy and hyperplasia of the centroacinar cells, and throughout the pancreas there appeared to be transitional stages between proliferating centroacinar cell clumps and Langerhans islets (Plate, Figs. 8 and 9).

The adrenals of the treated animals underwent considerable atrophy (160–255 mg.) as compared with the controls (335–380 mg.). Histologically, all layers of the cortex participated in this involution. It is especially noteworthy that the glomerulosa—which many investigators believe to be independent of hypophyseal regulation—was also very definitely involved in this compensatory atrophy. As an incidental observation it may be noted that in the cortex of the monkey adrenal comparatively large, homogeneous intercellular accumulations of strong PAS-positive material are frequently found. The origin and significance of this substance are not known, but in our series it was present both in the treated and in the untreated animals (Plate, Figs. 10 and 11).

The spleen underwent considerable atrophy in all the Me-F-COL-treated monkeys; its mean weight was 1.8 g. (1.3–2.0 g.), compared with 2.7 g. (2.3–3.1 g.) in the controls. Microscopical examination showed that the involution was principally due to a disappearance of the white pulp. Another striking histological change in all the treated animals was the deposition of PAS-positive hyaline material in the arteries of the white pulp. This was particularly conspicuous at the place of ramification into the penicilli, and often led to a complete obliteration of the lumen—with total loss of the vascular structure. PAS-positive material was also seen, free and within macrophages, in the interstitial spaces of the white pulp (Plate, Figs. 12 and 13). This process is presumably closely related to the hyaline changes of periarteritis nodosa; but, curiously, within the spleen infiltration with inflammatory cells was never conspicuous.

We saw no noteworthy changes in the thyroid and parathyroids of the treated animals. The anterior-lobe cells of the pituitary were perhaps somewhat atrophic, but hyalinization of the basophils, similar to that seen in Cushing's disease, was not observed. The thymus, on the other hand, became so atrophic in all monkeys treated with Me-F-COL that it was impossible to dissect the organ for accurate weighing. This involution, as well as the atrophy of the white pulp in the spleen, was presumably a manifestation of the glucocorticoid (lympholytic) potency of our steroid.

Discussion

These observations clearly indicate that Me-F-COL, a potent mineralocorticoid compound, can produce severe renal and cardiovascular changes in a primate. It remains to be seen whether the special "conditioning" which we used (unilateral nephrectomy and a comparatively high NaCl intake) is essential in order to obtain such effects in the monkey; however, our earlier work showed that in several other species (rat, hamster, fowl) such procedures sensitize but are not indispensable. The lesions in the kidney exhibited the histological characteristics of a

malignant nephrosclerosis, with changes typical of the Kimmelstiel-Wilson syndrome. At the same time there developed cardiac hypertrophy, an increase in blood pressure, widespread periarteritis nodosa, and a peculiar cystic transformation of Langerhans' islets. Since the last change was unexpected, we neglected to determine the glucose content of the blood and urine, and hence we do not know whether the monkeys became diabetic. Several earlier investigators observed minor changes in the Langerhans' islets of animals other than the monkey (rabbit, cat, dog)—especially after sensitization with alloxan or subtotal pancreatectomy—following heavy overdosage with cortisone, cortisol, the Δ^1 -corticoids, or A.C.T.H. (For literature see Houssay *et al.*, 1954; Penhos and Cardeza, 1956; Selye, 1950, 1951; Selye and Horava, 1952, 1953; Selye and Heuser, 1954, 1955–6.) But, so far as we are aware, this cystic change has not been previously produced with steroids in any species.

The average daily dose of Me-F-COL given to our monkeys during the 80-day observation period was 7.5 mg., and necropsy revealed that most of the injected hormone crystals remained under the skin, presumably because this steroid is very slowly absorbed. Consequently it is clear that only a fraction of the injected steroid was actually responsible for the production of these severe organ changes, although we cannot tell from our experiments the minimum amount required for the production of renal, cardiovascular, and pancreatic changes of this type.

Since in this experimental series the morphological organ changes were unaccompanied by signs of muscular paralysis, it is clear that the syndrome of malignant nephrosclerosis with periarteritis nodosa can result from overdosage with a steroid compound in a primate without the complicating signs of the periodic paralysis characteristic of primary aldosteronism.

There is no reason to believe that the adrenal cortex can produce steroids similar in their chemical structure to Me-F-COL. Still, we feel that our observations raise the question whether deviations from the normal pattern of steroidogenesis in the adrenal could result in the formation of corticoids having comparable biological actions. In any event, it is clear that the syndrome of generalized "hyalinosis" can occur in the primate as a result of corticoid overdosage, and that, contrary to common belief, periarteritis nodosa is not necessarily a manifestation of allergic hypersensitivity.

Summary

Experiments on unilaterally nephrectomized rhesus monkeys indicate that overdosage with comparatively small amounts of a new highly potent synthetic mineralocorticoid, 2-methyl-9(α)fluorocortisol (Me-F-COL), can produce severe malignant hyalinizing nephrosclerosis, with renal changes reminiscent of those seen in the Kimmelstiel-Wilson syndrome, cardiac hypertrophy, a rise in blood pressure, periarteritis nodosa, and a peculiar type of cystic transformation of Langerhans' islets.

This syndrome was not accompanied by the signs of periodic paralysis seen in monkeys overdosed with deoxycorticosterone and in patients with primary aldosteronism. It is concluded that a rather typical syndrome of malignant nephrosclerosis with periarteritis nodosa can be induced hormonally in the primate under conditions which bear no apparent relationship to allergic hypersensitivity.

Attention is called to the danger of producing similar changes by overdosage with 2-methyl-halo-corticoids in man, but further work will be necessary to establish with certainty whether endogenous secretion of corticoids can participate in the pathogenesis of malignant nephrosclerosis, the Kimmelstiel-Wilson syndrome, periarteritis nodosa, or Langerhans' islet changes in the human being.

As an incidental observation, it was noted that completely adrenalectomized monkeys given 2-8 mg. of Me-F-COL per day rapidly died showing a syndrome characterized by acute cardiovascular damage and leucocytic infiltrations, especially in the liver and kidney.

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HYPERPLASIA OF THE ADRENAL MEDULLA

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[WITH SPECIAL PLATE]

In every case in which hypercorticalism is present the question arises whether the increased function is caused by a tumour of the adrenal cortex or by hyperplasia. The occurrence of hyperfunction of the adrenal medulla, causing permanent or paroxysmal hypertension, has long been known. In most cases a phaeochromocytoma was thought to be the underlying cause. The number of cases in which such a tumour has been found and removed surgically is rapidly increasing.

In general, in discussing problems of the glands of internal secretion it can be stated that conditions which can be expected to exist as theoretical possibilities have a tendency to occur in practice. Such a theoretical possibility is clearly the existence of hyperplasia of the adrenal medulla as a counterpart to phaeochromocytoma and in analogy to the conditions found in the adrenal cortex. However, the existence of a clinical syndrome corresponding with this possibility has been greatly neglected, and has even been emphatically denied in many recent articles and textbooks discussing adrenal disease and especially hyperfunction of the adrenal medulla. The following is a case in point.

Case History

The patient, an unmarried woman, first noticed that she had become nervous, irritable, and intolerant to heat in 1936, when she was aged 17. These symptoms disappeared gradually. In 1950 she had for the first time during the night an attack of occipital headache, palpitations, and severe diffuse sweating. Since then she has had similar attacks with increasing frequency, usually lasting two or three hours. Usually the attacks started without known cause, about twice a week. Dyspnoea developed, but there was no marked loss of weight. The patient was admitted to another hospital in 1951, where she was found to have marked tachycardia (150 per minute), an increased basal metabolic rate (+52%), and hypertension (220/100 mm. Hg). The presence of a phaeochromocytoma was suspected. The usual tests for this disease gave no definite results, and treatment with antithyroid drugs had no effect. Perirenal insufflation with oxygen showed moderate enlargement of the left adrenal. On surgical exploration of the adrenals both glands appeared to be normal. No phaeochromocytoma was found in the adrenals or in the para-aortic tissues, and a biopsy of the left adrenal was performed. The only finding was some hyperplasia of the adrenal cortex. The possibility of a diencephalic lesion was discussed, and treatment with methylphenobarbitone and hexamethonium was instituted without benefit.

First Admission

The patient was first admitted to our department in 1953. She again had marked hypertension (200/120 mm. Hg), tachycardia (120-140 per minute), and a very high basal metabolic rate (+90%), without other clinical signs of hyperthyroidism. The blood pressure fluctuated markedly. Investigation with radioactive iodine showed normal thyroid function.

The frequency of the attacks increased, and during each attack she felt acutely ill. The attacks consisted of severe occipital headaches, palpitations, and excessive sweating,

Record of blood pressure and pulse rate during period March 26 to April 9, 1953. Shows one severe attack on March 31 with rise in blood pressure and tachycardia, and two minor attacks on April 4 and 6 with tachycardia but no rise in blood pressure.

with a pulse rate reaching 196 per minute. Often there was an increase in blood pressure, especially the systolic pressure (see Chart). Other signs were red blotching on the face, neck, and chest, mild dyspnoea (25-30 respirations per minute), and occasionally tremor affecting the whole body. During two attacks the blood sugar was determined and found to be normal (105 and 106 mg. per 100 ml.). The duration of the attacks varied from 15 minutes to half a day. During mild attacks the blood pressure was not increased. Pharmacological tests with piperoxan, phentolamine, histamine, and hexamethonium gave no indications of the presence of a phaeochromocytoma. Blood sugar tolerance was normal. Excretion of 17-ketosteroids was

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FIG. 1.—Kidney of normal control monkey from Group I.

(Figs. 2-9 are from non-adrenalectomized monkeys of Group II which received Me-F-COL. Sections stained PAS)

FIG. 2.—Showing pronounced hyaline necrosis with secondary inflammatory changes around hilar vessels of a glomerulus (centre of field) and presence of numerous hyaline casts which obstruct tubules ($\times 107$.)

FIG. 3.—Interstitial glomerulosclerosis with deposition of deeply tingible PAS-positive material in glomerular stroma. Some tubules lined exclusively by "clear cells." ($\times 107$.)

FIG. 4.—Pearl-like PAS-positive accumulations which virtually occlude certain glomerular capillaries, as in Kimmelstiel-Wilson syndrome. ($\times 107$.)

FIG. 5.—Branch of a coronary artery with marked intima proliferation (centrally from internal elastic membrane) limited to left of field. ($\times 90$.)

FIG. 6.—Branch of a coronary artery with intense infiltration of inner layers by PAS-positive hyaline material. ($\times 90$.)

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FIG. 7.—Another branch of coronary arterial system in which intima proliferation has progressed to a point where lumen is considerably reduced. ($\times 40$.)

FIGS. 8 and 9.—Langerhans islets with advanced cyst formation. Note also proliferation of centroacinar (light grey) cells in exocrine tissue. ($\times 108$.)

FIG. 10.—Section through entire width of adrenal cortex of an intact control monkey of Group I. Three layers clearly distinguishable; a darkly staining PAS-positive intercellular lake near right lower corner of field. ($\times 67$.)

FIG. 11.—Corresponding region of Me-F-COL-treated animal from Group II. Cortex atrophic and occupies only upper half (dark region) of field, outside medulla. Fasciculata and reticularis no longer clearly distinguishable, because of intense cell involution; glomerulosa also participates in atrophy. ($\times 67$.)

FIG. 12.—Malpighian corpuscle in spleen of an intact control animal. Lymphatic tissue around central artery well developed. ($\times 107$.)

FIG. 13.—Spleen of Me-F-COL-treated monkey from Group II. Lymphatic tissue has almost completely disappeared; two dark blocks of intensely PAS-positive intercellular material. ($\times 107$.)