Previously, this situation was treated exactly by QED, but only for the case of circular orbits (6).

Once again, Lieu and Axford enlisted FWW but introduced Compton corrections. First, momentum conservation requires that a scattered photon of laboratory frequency ω is related to an incident photon of frequency ω/η, where η is given to an accuracy of $1/\gamma^2$ by

$$\eta = 1 - \hbar\omega/\gamma mc^2 \qquad (2)$$

Note that η does not depend on any laboratory angle. Moreover, a scattered photon energy of $\hbar\omega \rightarrow \gamma mc^2$ results from an incident photon of infinite energy, implying that a spectral cutoff must exist at $\hbar\omega = \gamma mc^2$

Second, the Compton cross section must be used. Here a distinction is made between spinless and spin-½ particles. Lieu and Axford (*1*) published results that are valid for arbitrary planar orbits in a nonuniform magnetic field, with generalization to include three-dimensional orbits (5). A particularly fascinating point is that for $\hbar\omega/\gamma mc^2 << 1$, the differential number of emitted photons is simply given by its classical formula with the replacement $\omega \rightarrow \omega/\eta \approx \omega(1 + \hbar\omega/\gamma mc^2)$. This well-known first-order quantum correction (*3*) can now be identified with electron recoil accompanying the scattering of equivalent photons. For a full comparison with QED, however, it is necessary to adopt the restricted case of a circular orbit, because QED has no exact results for more general situations.

In the case of orbital radiation from a spinless charge, there is complete agreement with QED. For spin-½ particles, the agreement is not complete, but the two theories are indistinguishable until $\gamma B/B_c \sim 10$. Moreover, as announced by Lieu at the SPIN94 conference, this discrepancy is now removed (*7*). The source of the problem has to do with spin-flip effects.

It was predicted by Sokolov and Ternov (8) that electrons should become spin-polarized antiparallel to the field as a result of spin-flip synchrotron radiation. The effect was first observed in 1970 (9) and is routinely seen at the storage rings like the Large Electron-Positron Accelerator (LEP) and the Hadron-Electron Ring Accelerator (HERA), where it is now possible to make longitudinally polarized electrons for high-energy experiments (*10*).

Because the electron "spin" is usually taken to mean the spin angular momentum in the rest frame of the particle, it would be illuminating to calculate the entire spin-½ emissivity in this frame with the Lieu-Axford formalism. However, originally Lieu and Axford (*1*) did not calculate spin-flip effects because they used the spin-averaged Compton cross section (*11*). Instead, the correct procedure will involve the spin-dependent cross section, which contains a simple magnetic dipole (that is, $\mathbf{s}\cdot\mathbf{B}$) interaction term, followed by coherent integration of the amplitudes along the orbit. One can then arrive at a general emissivity formula valid for spin-½ particles, which reduces exactly to the QED result for circular orbits.

Apart from the beam polarization effect already discussed, another potentially important application of this approach has to do with the so-called "beamstrahlung" in high-energy linear colliders, where one beam is deflected significantly by the very strong collective fields of the colliding beam, with consequent radiative deceleration. The fields of concern reach the quantum limit defined in Eq. 1. In particular, because the field gradient can be large, the standard QED formula for circular orbits is not very useful. Perturbation methods have been used to treat small gradients (*12*), but the general formula in (*1*) provides, in principle, a new framework for going beyond this result. There is also relevance to astrophysics because the quantum limit of concern can be reached in pulsars and possibly in the jets of active galactic nuclei (AGN). In the former, Eq. 1 becomes relevant at the pulsar surface, where the magnetic field reaches 10^{12} G, and further out, where the field remains quite high and γ may become large. In the latter, the limit given by Eq. 1 is likewise reachable for AGN jets near the central engine (believed to be a black hole), where fields on the order of 10^3 G are expected and electrons of energy approaching 10^{18} eV could arise by pion production from a directly accelerated proton, if electrostatic potentials as estimated by Lovelace *et al.* (*13*) occur. Finally, the work of Lieu and Axford may lead to new insights on the problem of radiation from charges accelerated by nonelectromagnetic forces.

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A Rising StAR: An Essential Role in Cholesterol Transport

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The biosynthesis of the steroid hormones—estrogens, glucocorticoids, mineralocorticoids, and androgens—starts with cholesterol. Within the mitochondria of the adrenal cortex, gonads, and placenta, cholesterol is converted to pregnenolone by the side chain cleavage, cytochrome P450 (P450scc) This side chain cleavage reaction is the rate-limiting step; however, it is not the complex catalytic mechanism that is rate limiting. Rather, mobilization of cholesterol from lipid stores to the vicinity of P450scc in the inner mitochondrial membrane controls steroid synthesis. In this issue of *Science* (page 1828), Lin and coworkers (*1*) report that the underlying mutation in patients with congenital lipoid adrenal hyperplasia is in the recently discovered steroidogenic acute regulatory protein (StAR) (*2*) and that StAR is now implicated in this mobilization process. The black box of cholesterol transport within steroidogenic cells may soon release its secrets.

Steroid hormone biosynthesis couples the action of peptide hormone receptors with that of nuclear, zinc-finger receptors. Peptide hormones from the anterior pituitary regulate steroidogenesis through adenosine 3',5'-monophosphate (cAMP), leading to the production of steroid ligands for the nuclear receptors. For example, adreno-

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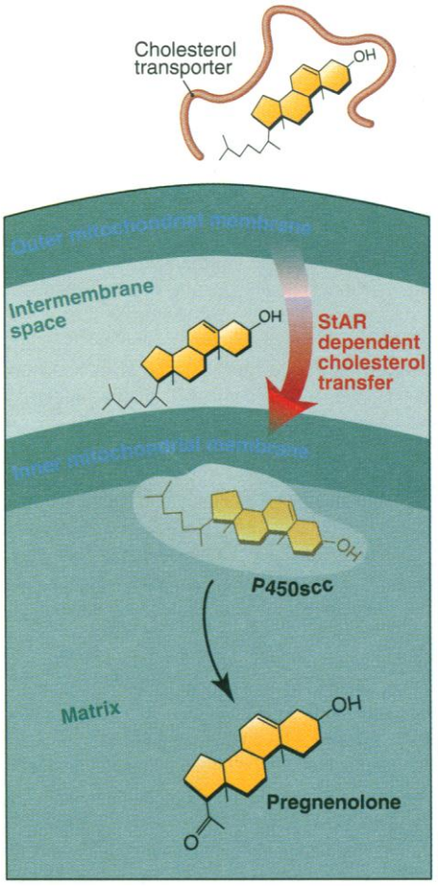
corticotrophic hormone (ACTH) binds to its cell surface receptor on adrenocortical cells and activates adenylate cyclase, which in turn elevates intracellular cAMP. Cyclic AMP then does two things, at least with respect to steroid synthesis: On a slower time scale, it causes transcriptional activation of genes encoding steroid hydroxylases and accessory proteins. More immediately, within seconds or minutes, cAMP activates the hydrolysis of ester functions from cholesterol esters in lipid droplets, and the free cholesterol is transported to the mitochondrion. Once cholesterol reaches the mitochondrion, it must traverse the outer membrane and the intermembrane space to reach the inner mitochondrial membrane (*3*) where P450scc resides, a process that remains poorly understood. Protein synthesis inhibitors such as cycloheximide block hormone-dependent steroid production (*4*), but the accumulation of cholesterol in the outer mitochondrial membrane or the P450scc activity itself is unaffected (*5*). Thus, for many years experiments have been carried out to identify the "labile protein factor" required for cholesterol transport to the inner mitochondrial membrane, leading to a number of candidate proteins (*6*).

StAR—an acutely regulated, cycloheximide-sensitive, mitochondrial protein that activates steroidogenesis in heterologous systems (*1*,*2*)—has been recently described and put forward as a promising new candidate. However, the precise subcellular localization of StAR and its role in cholesterol movement within the mitochondrion have not been clear. Now, from a quite different direction—namely, characterization of the molecular basis of a specific form of congenital adrenal hyperplasia—Lin and co-workers provide direct evidence for an essential role of StAR in steroidogenesis.

The congenital adrenal hyperplasias are a group of autosomal recessive diseases resulting from blockade of the steps in normal steroid hormone synthesis. In most cases the defect results from mutations in a specific gene encoding one of the enzymes in the steroidogenic pathways. However, no mutations have been detected in patients with congenital lipoid adrenal hyperplasia, a form of the disease associated with a deficiency of P450scc activity (*7*). In a patient homozygous for congenital lipoid adrenal hyperplasia, but having no mutation in the p450scc gene (CYP11A), testicular mitochondria had readily detectable P450scc activity, even though these patients cannot synthesize steroid hormones (*8*). Several



Putative site of StAR action: Movement of cholesterol from the outer mitochondrial membrane across the intermembrane space to p450scc in the inner membrane. The cholesterol transporter is hypothetical.

such patients in Japan, France, and the United States have been examined without evidence of gene mutation. This finding has been puzzling because in all other forms of congenital adrenal hyperplasia, a mutation in a gene encoding a steroidogenic enzyme is readily observed to account for the symptoms. Lin and colleagues predicted that the defect in congenital lipoid adrenal hyperplasia might reside not within P450scc but rather in one of the proteins of cholesterol transport. Indeed, as shown on page 1828, the defect is found in the accessory protein StAR rather than the hydroxylase itself, thereby explaining why mitochondria from such patients have readily detectable P450scc activity when substrate is added exogenously. Thus, these findings reveal not only the molecular basis for this rare genetic disease, an achievement in itself, but also provide much needed functional evidence for StAR's critical part in regulation of cholesterol availability in the mitochondria of steroidogenic cells.

The timely cloning and expression of StAR by Clark and Stocco (*2*) made the investigation of StAR in patients with congenital lipoid adrenal hyperplasia an attractive avenue. Mutations leading to premature stop codons in StAR are associated with an absence of steroid hormone production. Heterologous expression of the mutant forms of StAR confirm that these truncated proteins cannot support pregnenolone production. Interestingly, immunoblot analysis of the heterologously expressed mutant proteins suggests that premature truncation prevents proteolytic processing at the amino terminus, a normal step in the mitochondrial uptake of StAR.

StAR's essential role in steroidogenesis raises new questions about the details of the process. Does StAR bind cholesterol and transport it within mitochondria? Or does StAR facilitate contact between the two mitochondrial membranes, making passive movement of cholesterol across a concentration gradient from the outer to the inner membrane possible? What is the basis of the sensitivity of StAR to protein synthesis inhibitors? Even when we know the exact function of StAR, we will likely not have a complete understanding of cholesterol transport in steroidogenic tissues. Other proteins may participate and cholesterol movement from lipid stores to the outer mitochondrial membrane remains ill defined. Nevertheless, characterization of the mechanism by which StAR functions in adrenal and gonadal steroidogenesis surely provides much needed new insight into this important process that has been refractory to biochemical analysis for many years.

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