The story about our Cortef® products

Systemic: administered internally; circulates throughout body

Oral administration
Tablets

Injection
Intramuscular (under clinical investigation)
Intravenous (under clinical investigation)

Topical: applied externally

Skin

Ophthalmic: applied to the eye

Eye

Shortly before Christmas, a lady living in Mr. Shasta, California stopped at her doctor's for treatment of a swollen, painful eye. The physician suggested a new product he was evaluating for The Upjohn Company. Neo-Cortef® drops. Early in January this same lady wrote to the physician to say: 'What a wonderful drug! And so pleasant to use. I'm so glad I stopped and found out about it. It was my best Christmas surprise.'

What is this compound called Cortef?

Cortef® is the trademark of Upjohn for its brand of hydrocortisone—also known as Compound E or cortisone. In fact, the two are so closely related that they are practically identical in chemical structure. The difference occurs at the non-famous seventh position in the molecular ring where cortisone has an oxygen atom and hydrocortisone has, in addition, a hydrogen atom. Both cortisone and hydrocortisone are steroids which were originally isolated from adrenal glands, but are now manufactured synthetically. Because both cortisone and hydrocortisone suppress signs and symptoms of (but do not cure) inflammatory conditions they are sometimes known as the "adrenal twins." Cortef® is the more active and therein lies.

The difference between the "adrenal twins."

Studies so far indicate that the effect of 50 milligrams of hydrocortisone equals that of 100 milligrams of cortisone acetate. The other striking advantage of Cortef® is the strong anti-inflammatory activity it displays on the skin. These points in its favor.

Cortef® has several uses.

Physicians may prescribe it for rheumatoid arthritis. Helpful in this connection are the facts learned about the therapeutic usefulness of cortisone because they apply in principle to Cortef® also. Dermatologists may find Cortef® even more interesting as it is so useful in treating allergic eczema, poison ivy, and other skin conditions as further developed. Since hydrocortisone relieves the signs of inflammation (but tends to cause the spread of infection), and since many skin diseases are apt to become infected, experiments to combine Cortef® with the antibiotic neomycin to fight infection resulted in

Development of Neo-Cortef® products.

The first antibiotic-hydrocortisone combination in ointment form to appear on the market, Neo-Cortef® offers a dual attack against inflammation and infection. Neomycin was the antibiotic chosen for combination with Cortef® because experience has shown its range of antibacterial activity to be very broad and, since it is not used internally for severe infections, problems of sensitivity are not so apt to be created.

The development of hydrocortisone was forecast at the time cortisone was announced. Its chemical synthesis had not yet been mastered, however, and the question stood

How do we get Cortef?

Literally, the work of hundreds of Upjohn people went into the development of Cortef®. Their activities were so interwoven as to be almost inseparable. The story which follows establishes the pattern of development in its broadest outline only.
Teamwork in Research produced hydrocortisone as a pure chemical.

The beginning of the hydrocortisone story lies in the Company's decision to look for a practical method of producing the hormone. The development program which followed yielded two good processes and placed Upjohn in the fortunate position of having a choice to make.

Several factors made it advisable to set aside the biochemical process in favor of the chemical process represented below. Take-off for this research was the fermentation process which had been developed for cortisone manufacture. This was integrated with a complicated series of

Rex Mann and Eldon Nelson, Department of Endocrinology Research, Gordon French, antibiotics Production, and Joe Albert, Harrison Nelson, and Fred Hansen, Department of Antibiotics Research, represent those who developed a biochemical process, left, set aside, for hydrocortisone. It was this method which produced the first hydrocortisone on a large scale.

"This is what we want. How do we get it?" question Department of Chemistry's John Hegg, Barney Magarlein, Bill Schneider, and Art Finito. Before and during experimentation, program for the chemical process was evaluated and integrated at planning sessions like this.

Chemistry's Gus Fendley and Phil Best look for answers to some problems in the library. This means a saving to them of costly experiment time, and saves money for the Company as well.

Many answers this paper on experiments, one vital painstaking care. In a Chemistry lab, Rob Jackson and Anna May Searcy concentrate on Alan Nathan's reading of a melting point.

180
Fermentation was the key step which redirected the line of chemical exploration.

Chemical steps to transform the basic sterol raw materials into hydrocortisone. From the coordinated work of many people were drawn the steps that finally fell into place to produce this microbiological-chemical process.

Assays tell the story of an experiment’s success, for it is this tool that gives the final evaluation of a material’s identity, purity, etc. In the case of a new compound such as an hydrocortisone intermediate, however, assays, too, must be devised. Some of this research was done by Tom Chubbs, Physics Department.

Once crystals were obtained in small-scale experiments, Paul Marlett, Don Myers, and Bill Wetherell tackled developmental work needed to adapt methods to larger-scale experiments.

Numerous hurdles—like this one between Gene Weeduff, Head of Department of Patents and Technical Information, Garson Herrschel, Head of Patent Law Department, and Chemistry’s Vern McIntosh and Frank Lincoln—were necessary to build a web of patent protection around our hydrocortisone developments.
Development of pure hydrocortisone tells only part of the story.

Objective at this point was to produce large quantities of the chemical quickly so that experiments with dosage forms could get underway. Problems were foreseen through foresight of management who authorized a large investment in Pilot Lab scale-up equipment even before chemists had completely developed the synthesis. This faith and advance planning (installation of equipment actually began the middle of 1952) has enabled the Pilot Lab to meet all production requirements for hydrocortisone to date. Among the many people who had a part in the design and installation of equipment on operating platforms above were Pilot Lab’s Lab Bedell and Steamfitters’ Supervisor Chuck McKenzie, left, Dick Roundhouse and Al Boursame.

Engineering-wise, one of the biggest feats in scale-up activities was the development of safe procedures for handling the very hazardous reagent, anhydrous ethyl ether. Since elimination of this material from the process was impossible, it became essential that we learn to get along with large amounts of it safely. Special hoppers for Pilot Lab bottles, which Jim Marsha and Alben Drake examined, is mechanical contribution to safe handling techniques.
Appropriate dosage forms had to be created before the hormone would be useful.

At the moment pure hydrocortisone becomes available, projects were underway to put
them into a usable form for the physician. Medical experience and probable uses for
the drug suggest the pharmaceutical vehicles that should be investigated. It is
Pharmaceutical Development’s job to produce those formulations. Past experience
proves a valuable aid, but each new formulation carries its own problems that must
be solved if safe, potent, stable, attractive preparations are to be created. Some of
those involved in this search are shown below.

Before any preparation may go
for clinical investigation, its
safety must be assured by the
Department of Pharmacology.
Purpose of clinical in-
vestigation is evaluation by
specialists in the field. On the
basis of their appraisal these
things may happen to a formu-
lation: acceptance, rejection, fur-
ther developmental work and
more testing. Marion Dyk-
shoorn, Dan Moolendam, and
Dale Redeker have already sent
centuries of Cortef samples to
clinics all over the country. By
meeting the rigors of this inves-
tigation, nine Cortef products
up to date, have received the nod
for full-scale production.
Refinements, then full-scale production have thus far yielded nine

Representing ointment production, Tom Richmond weighs assembled Neo-Cortel ingredients.

Lee Leamor portrays early stage in tablet manufacture—blending powdered materials in 600 lb. mixer.

Cortel ointments 1%, 2.5%
Neo-Cortel ointments 1%, 2.5%
Neo-Cortel sulfathalidinic ointment 1.5%

Cortel tablets 5 mg., 10 mg., 20 mg.

Looking at the total picture, Pharmaceutical Development's job of transforming the hormone into products was certainly one of the pivot spots. Basically, development hinged on the perfection of a vehicle, or base, to carry the active ingredient as well as the establishment of a procedure for mixing the two. For instance, Neo-Cortel eye drops are the first, and only, eye suspension that Upjohn has distributed nationally. Two years were needed to develop a vehicle which would give a suitable suspension of hydrocortisone powder. The research was guided by three fundamental requirements: that the suspension be sterile, easily reconstitutable, and non-irritating. Jack Dale has personally tested many batches of cyclops to check the presence of irritating qualities. In the development of ointments and tablets, past experience has been a helpful guide. As the various Cortel products have taken the step to full-scale production, the men in Pharmaceutical Development have aimed by to pool their experience with the know-how of the Production staff.

Cortel was introduced in August 1955 at a reduction of about twenty percent below the currently prevailing price.
Cortef products for Upjohn to market.

In sterile area, George Kramer runs suspension through rolled mill to disperse particles.

Neo-Cortef drops 1.5%

Cortef ointments gave Control some trouble. Colorimetric assays (to determine amount of Cortef) were developed and Bill West now runs a series almost daily.

Appeal, flexibility, temper-proof bottles were package-design objectives. Lock-in feature of ointment packages is shown by Fred Bither, Packaging Development Head.

This reduction and Cortef's greater potency allow the doctor to prescribe Cortef at about the same price as cortisone.

Many groups, probably as numerous as are the groups in the Company, had a part in getting Cortef into the hands of physicians. Medical, for instance. In the beginning, the staff pointed out the importance of hydrocortisone to medicine. As dosage forms took shape, the staff evaluated them clinically. Finally, F.D.A. clearance of Cortef was obtained by this group. In simplified form, then, this is the story that has made possible treatment results like those to the right.

Before | After

After just five days treatment with Neo-Cortef, the swelling and inflammation that had all but closed this patient's eye was noticeably improved.