from: The Upjohn News, April 1954

The story about our Cortef *products*

Systemic *administered internally: circulates throughout body*

Oral administration

Tablets

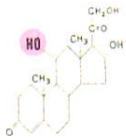
Injection

***Intramuscular* (under clinical investigation)**

***Intravenous* (under clinical investigation)**

Topical: *applied externally*

Ophthalmic: *applied to the eye*



Shortly before Christmas, a lady living in Mt. 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* Acetate 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 F. It is a chemical relative of Compound E or cortisone. In fact, the two are so closely related as to be almost identical in chemical structure. The difference occurs at the now-famous eleventh position in the molecular ring where cortisone has an oxygen atom and hydrocortisone has, in addition, an 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 to date indicate that the effect of 70 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 its usefulness in treating allergic eczema, poison ivy, and other skin conditions is 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

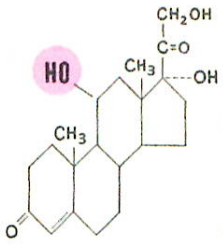
Development of Neo-Cortef products.

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

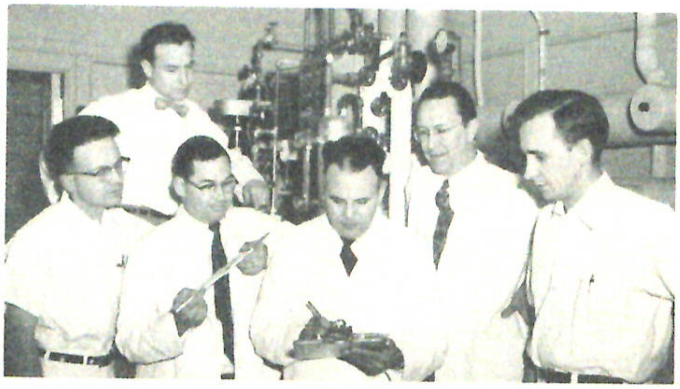
How do we get Cortef?

Literally, the work of hundreds of Upjohn people went into the development of *Cortef*. Their activities were so intertwined as to be almost inseparable. The story which follows establishes the pattern of development in its broadest outline only.



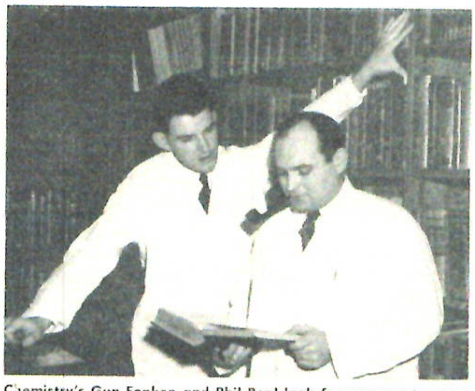
Teamwork in Research produced hydrocortisone as a pure chemical.

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 Nielson, Department of Endocrinology Research, Gordon French, Antibiotics Production, and Joe Alberti, Harrison Nelson, and Fred Hanson, Department of Antibiotics Research, represent those who developed a biochemical process, later 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 Hogg, Barney Magerlein, Bill Schneider, and Art Hanze. Before and during experimentation, program for the chemical process was evaluated and integrated at planning sessions like this.

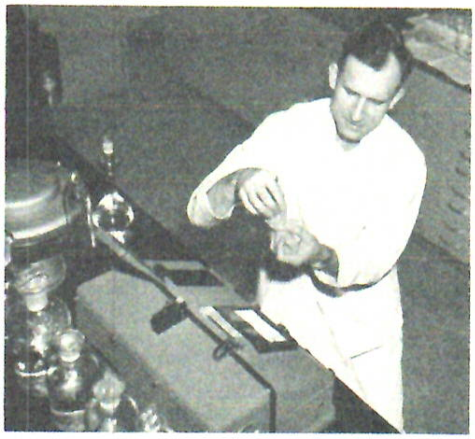


Chemistry's Gun Fonken and Phil Beal look for answers to some problems in the Library. This means a saving to them of costly experiment time, and saves money for the Company as well.

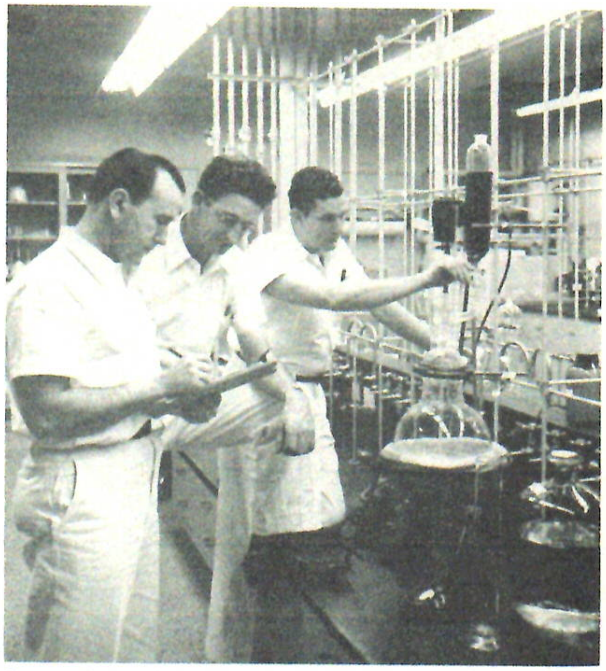
Many answers still depend on experiments, done with painstaking care. In a Chemistry lab, Bob Jackson and Anna Mae Searcy concentrate on Alan Nathan's reading of a melting point.

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.

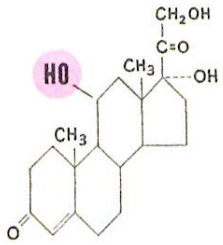


Assays tell the story of an experiment's success, for it is this tool that gives the final evaluation of a material's identity, purity, etc. In the case of a new compound such as an hydrocortisone intermediate, however, assays, too, must be devised. Some of this research was done by Tom Chulski, Physics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

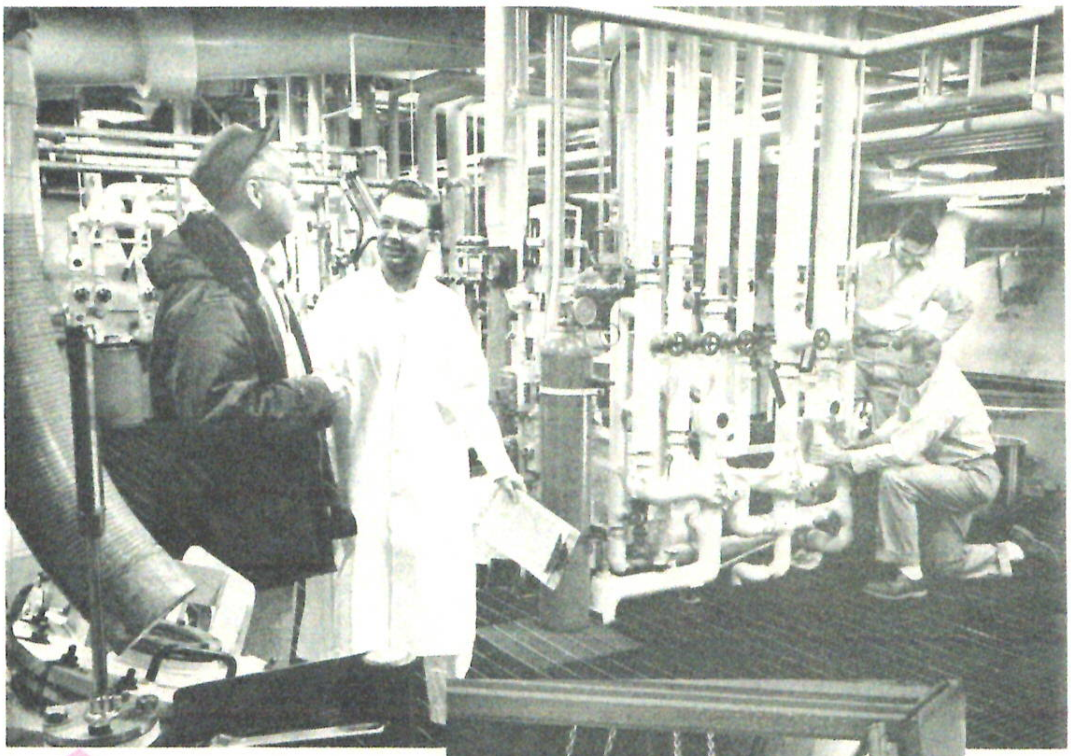


Once crystals were obtained in small-scale experiments, Paul Marlatt, Don Myers, and Bill Wetherall tackled developmental work needed to adapt methods to larger-scale experiments.

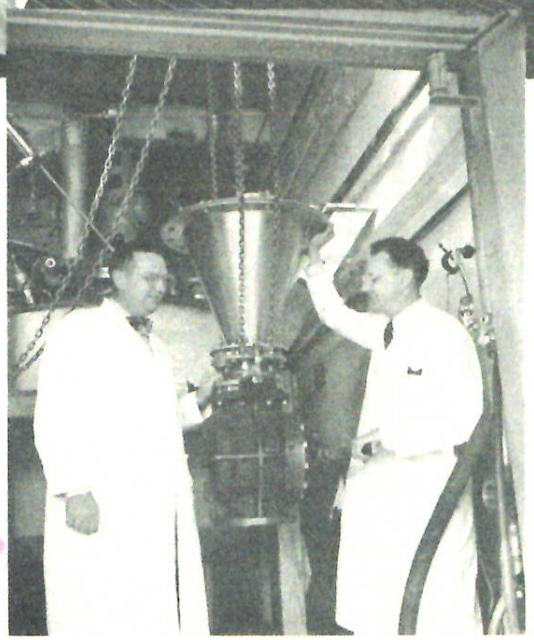
Numerous huddles—like this one between Gene Woodruff, Head of Department of Patents and Technical Information, Gordon Hueschen, Head of Patent Law Department, and Chemistry's Vern McIntosh and Frank Lincoln—were necessary to build a web of patent protection around our hydrocortisone developments.



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 lessened 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 platform above were Pilot Lab's Bob Bedell and Steamfitters' Supervisor Chuck McKenzie, left, Dick Roundhouse and Al Boersma.



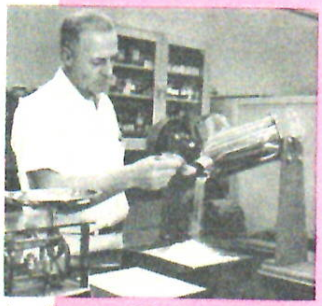
Engineering-wise, one of the biggest feats in scale-up activities was the development of safe procedures for handling the very hazardous reagent, anhydrous ethyl ether. Since elimination of this material from the process was impossible, it became essential that we learn to get along with large amounts of it safely. Special hopper for Pilot Lab kettles, which Jim Harkema and Alden Drake examine, is mechanical contribution to safe handling techniques.

Appropriate dosage forms had to be created before the hormone would be useful.

Correlation between Clinical Investigation, headed by Hal Hailman, left, and Pharmaceutical Development represented here by Bob Himelick and Walt Enz, Department Head, is evidenced as experimental dosage forms of the drug—now named Cortef—shuttle back and forth.

At the moment pure hydrocortisone became available, projects were underway to put them into useable 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 these 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.

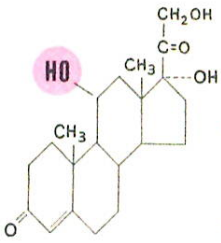
Sven Rundman, Lee Macdonald, ointments



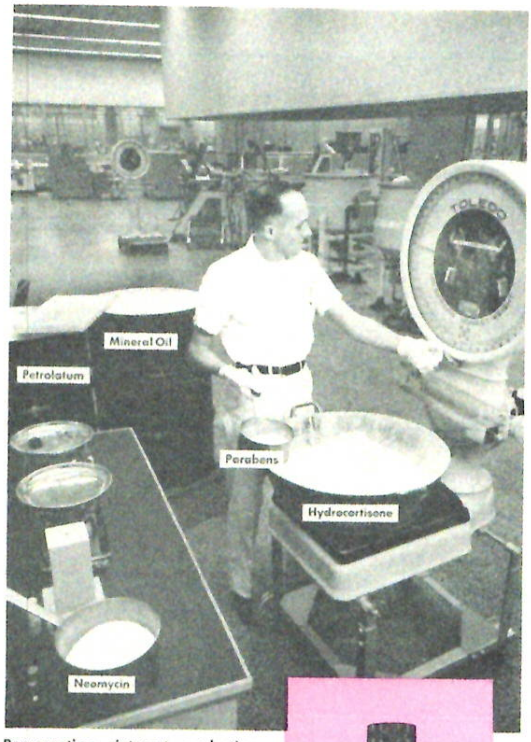
Jerry Pleyte . . . tablets

Jack Dale . . . sterile preparations

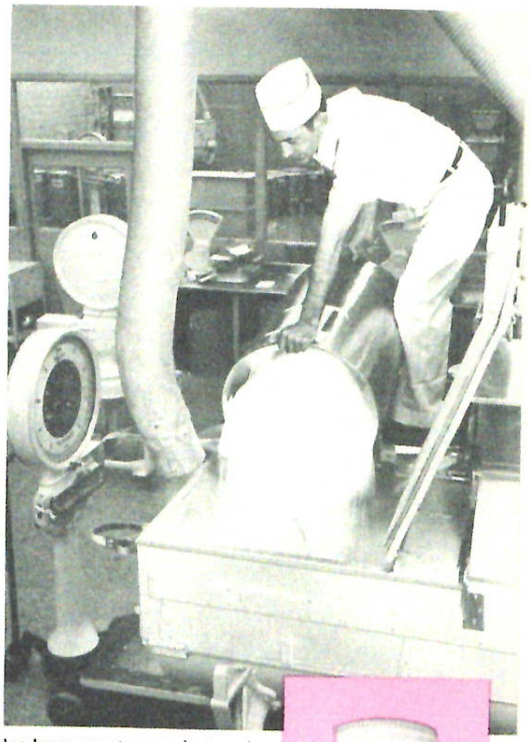
Before any preparation may go for clinical investigation, its safety must be assured by Department of Pharmacology Research. Purpose of clinical investigation is evaluation by specialists in the field. On the basis of their appraisal three things may happen to a formulation: acceptance, rejection, further developmental work and more testing. Marian Dykshoorn, Don Musselman, and Dale Redeker have already sent hundreds of *Cortef* samples to clinics all over the country. By meeting the rigors of this investigation, nine *Cortef* products, 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-Cortef* ingredients.



Leo Lemmer portrays early stage in tablet manufacture—blending powdered materials in 600 lb. mixer.

Cortef ointments 1%, 2.5%
Neo-Cortef ointments 1%, 2.5%
Neo-Cortef ophthalmic ointment 1.5%

Cortef 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-Cortef* 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 resuspendable, and non-irritating. Jack Dale has personally tested many batches of eyedrops to check the presence of irritating qualities. In the development of ointments and tablets, past experience has been a helpful guide. As the various *Cortef* products have taken the step to full-scale production, the men in Pharmaceutical Development have stayed by to pool their experience with the know-how of the Production staff.

Cortef was introduced in August 1953 at a reduction of about twenty per cent below the currently prevailing price.

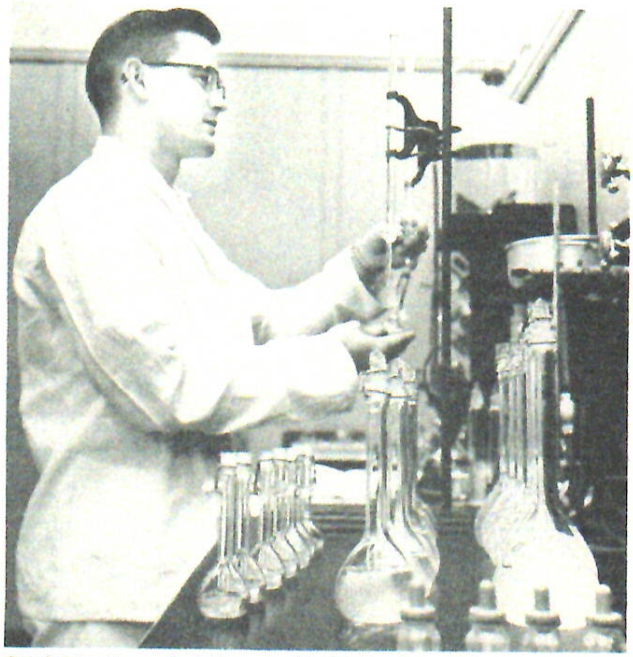
Cortef products for Upjohn to market.

In Sterile area, George Kramer runs suspension through colloid mill to disperse particles.

Neo-Cortef drops 1.5%

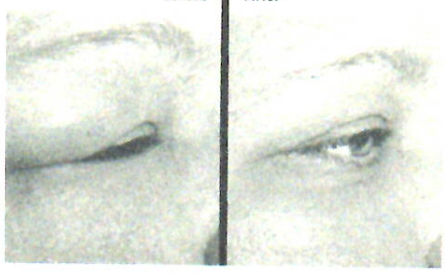
This reduction and *Cortef's* greater potency allow the doctor to prescribe *Cortef* at about the same price as cortisone.

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.



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



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