possible chemical interaction between actinomycin D and DMBA were negative. Thus the presence of 13.9 μg of actinomycin D per milliliter did not increase the solubility of DMBA in 0.01M NaCl, 0.001M NaH_2PO_4 (pH 7.4), and equimolar amounts of DMBA and actinomycin D in 25 percent acetone did not affect the absorption spectra of either between 325 and 500 mμ. Actinomycin D does not exert its action by stimulating the removal of DMBA from the skin. Thus, in the presence or absence of actinomycin D, more than 90 percent of DMBA labeled with carbon-14 disappeared from the skin 24 hours after application.

Our results suggest that the early biochemical events of skin tumorigenesis by DMBA are dependent on DNA-directed RNA synthesis. Thus the carcinogenic activity of DMBA is dependent on the presence of genetic activity. Whether the dependence is related directly to the RNA synthesized or to subsequently synthesized protein is unknown.

A single administration of methylcholanthrene, another carcinogenic polycyclic hydrocarbon, increases the amount of activity of several liver microsomal enzyme systems (*5*) and the benzopyrene hydroxylase activity in several rat tissues other than liver (*6*). Mechanism studies have shown that these effects are prevented by actinomycin D and puromycin (*7*). Furthermore methylcholanthrene increases the incorporation of amino acid into the liver microsomes (*8*), the amount of RNA in the nuclei of liver cells, and the "messenger RNA activity" of the nuclear RNA as measured by its activity in stimulating the incorporation of phenylalanine-C^{14} in an *Escherichia coli* system (*9*).

These findings (*5–9*) have led to the hypothesis (*7–9*) that early events in chemical carcinogenesis are alterations in the expression of specific genic information, that is, in the normal "gene-action systems," a term used by Waddington (*10*). Monod and Jacob (*11*) previously made a similar suggestion on theoretical grounds derived from their classical studies on the gene-action systems of microorganisms.

Transitory contact with a carcinogen may induce the synthesis of RNA and protein molecules that alter cellular environments in a specific manner. The alteration may be permanent and represent "initiation." As a result of appropriate interlocking of gene-action systems, the new environments may inactivate progressively those genes necessary for normal tissue function and activate the gene-action systems that characterize the developing tumor cell or the preneoplastic state. In certain systems, such as the one we used, the progression may require a promoting agent. In others, it may not. If a carcinogen-specific alteration in the expression of genic information is indeed the nature of "initiation," then a blocking of all gene expression, that is, DNA-dependent RNA synthesis, would prevent this process. We interpret our results to support the hypothesis that alterations in gene-action systems are the early biochemical events of carcinogenesis.

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References and Notes

1. J. C. Mottram, *J. Pathol. Bacteriol.* **56**, 181 (1944).
2. I. Berenblum and P. Shubik, *Brit. J. Cancer.* **1**, 383 (1947); ——— *ibid.* **3**, 109 (1949); ——— *Brit. Med. Bull.* **4**, 373 (1947).
3. H. Falk and P. Kotin, *Clin. Pharmacol. Therap.* **4**, 88 (1963).
4. E. Reich, R. M. Franklin, A. J. Shatkin, E. L. Tatum, *Proc. Natl. Acad. Sci. U.S.* **48**, 1238 (1962).
5. A. H. Conney, E. C. Miller, J. A. Miller, *Cancer Res.* **16**, 450 (1956);———*J. Biol. Chem* **228**, 753 (1957); A. H. Conney, J. R. Gillette, J. K. Inscoe, E. R. Trams, H. S. Posner, *Science* **130**, 1478 (1959).
6. L. W. Wattenberg and J. L. Leong, *J. Histochem. Cytochem.* **10**, 412 (1962).
7. H. V. Gelboin and Blackburn, *Cancer Res.* **24**, 356 (1964).
8. H. V. Gelboin and L. Sokoloff, *Science* **134**, 611 (1961); H. V. Gelboin and N. Blackburn, *Biochim. Biophys. Acta* **72**, 657 (1960); H. V. Gelboin, *ibid.*, in press.
9. L. Loeb and H. V. Gelboin, *Nature* **199**, 809 (1963); H. V. Gelboin and L. Loeb, in preparation.
10. Waddington's term to denote the "whole series of biochemical processes which lead from a gene to the phenotypic character by which it is recognized."
11. J. Monod and F. Jacob, *Cold Spring Harbor Symp. Quant. Biol.* **28**, 389 (1961).
12. We thank D. Morgan and H. Waters for valuable technical assistance.

20 July 1964

Staphylococcus aureus UC-18: Agent of Nosocomial Infections

Abstract. *A new strain of* Staphylococcus aureus, *implicated in severe "hospital-acquired" infections, has been recognized and identified. This strain is characterized by lysis with a recently isolated bacteriophage, UC-18. Resistance to penicillin, streptomycin, and tetracycline combined with widespread prevalence in the hospital environment make* S. aureus *UC-18 a significant contributor to endemic staphylococcal disease in hospitals.*

Recognition and identification of a new strain of *Staphylococcus aureus* implicated in severe "hospital-acquired" infections is of profound epidemiologic significance. Isolates that cannot be typed at routine test dilution of the standard international set of phages are encountered frequently, the percentage varying with the source of the isolates. A higher percentage is obtained from the environment than from clinical material. In an effort to further define these isolates that cannot be typed, phages at concentrations 1000 times the routine test dilution were included in the daily typing procedure during 1961 at Peter Bent Brigham Hospital.

A new phage pattern soon became apparent in isolates recovered from wound infections, burns, and blood cultures, as well as from volume-air samples and settling plates in the hospital wards. These could not be typed at routine test dilution, with inhibition by group III phages 47/53/54/75/77/42B /83A/83B in varying combinations at 1000 times the routine test dilution.

Staphylococcus aureus 80/81 strains had never predominated in our surgical-wound infections. In a study of 250 surgical procedures, strains 80/81 were recovered only twice from wounds. Since in each case the patient himself had been a carrier before surgery, it is possible that the source of infection was endogenous.

Isolates that could not be typed at routine test dilutions, but were inhibited by group III phages, were seen so consistently that they were saved for future phage isolations.

In June 1963 Altemeier and others (*1*) reported the isolation of a new phage, UC-18, which lysed *S. aureus* strains recovered from cases of enterocolitis. We secured this phage and its propagating strain from Dr. Hill at the University of Cincinnati; it was added to the 28 phages routinely used in our daily typing. In addition to the phages of the international set, the following phages are used at Peter Bent Brigham Hospital: 83A, 70, 73, 42B, 83B, 47C, 82, and UC-18.

Of the 114 isolates saved over a period of a year and characterized by

inhibition with group III phages at 1000 times the routine test dilution, 111 (97 percent) could be typed with UC-18 at routine test dilution. The sources of the isolates varied; 76 were from the hospital environment, 35 were from infections in patients.

During the past 5 months this phage pattern has figured prominently among our isolates capable of being typed. A total of 249 isolates have been lysed by UC-18. Of the 249 cultures, 203 (82 percent) were lysed by UC-18 alone; 46 (18 percent) were lysed by UC-18 in combination with other phages at routine test dilution. Ninety-seven were from the environment, 113 were from patients and personnel in our own hospital, while 39 were from patients from four other hospitals—three in the Boston area and one in Worcester, Mass. Thus, if only routine test dilutions had been used, 203 isolates would not have been identified with the standard set of typing phages.

Of the cultures from patients, one-third of the isolates came from wounds and another third from nose and throat cultures; the remainder came from miscellaneous sources, urine, blood, stool, sputum, and burns. The wounds were predominantly postoperative infections that occurred on surgical services. There has been a series of infections following orthopedic procedures, open heart surgery, and renal transplantation. The body surfaces of six recently burned patients were colonized by this strain.

We were able to make daily bacteriological studies of a patient with 60 percent of her body surface afflicted with second and third degree burns. On admission, her nasal cultures showed only *S. epidermidis*, and her skin surfaces yielded only *S. epidermidis* and *Bacillus cereus*. One week after admission, a culture of the bottom bed sheet and pillow case yielded one colony each of *Staphylococcus aureus* UC-18. On the following day *S. aureus* UC-18 was recovered from her left nostril and, on subsequent days, from the right nostril also; it was recovered from her burned surfaces on her 11th hospital day, and daily thereafter. From her 7th hospital day, environmental cultures consistently yielded *S. aureus* UC-18 on her bedding, on settling plates, and in volume-air samples taken by the Wells air centrifuge. No other strain of *S. aureus* was ever recovered from her body surfaces or her environment. A biopsy, the full thickness of the skin, was taken on the 11th day after the burn to determine the extent of penetration by staphylococci and other organisms. Gram-negative rods and *S. aureus* UC-18 were present, even in the deep layer of the dermis. The three organisms consistently recovered until the death of the patient were *Pseudomonas aeruginosa, Klebsiella aerobacter*, and *S. aureus* UC-18.

At present approximately 10 percent of the staphylococci isolated in our laboratory are of the UC-18 phage pattern; they are resistant to penicillin, tetracycline, and streptomycin.

On the other hand, no UC-18 strains were encountered in isolates from 150 high school students who had no association with hospitals.

All cultures of *S. aureus* UC-18 recently isolated have come from patients, carriers, or other hospital environments. It appears to be a strain indigenous to hospitals and capable of producing infection in burns and surgical wounds.

The addition of UC-18 phage to the standard international set of typing phages is therefore recommended to reduce significantly the number of untypable staphylococci recovered from hospital sources (*2*).

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References and Notes

1. W. A. Altemeier, R. P. Hummel, E. O. Hill, *Ann. Surg.* **157**, 847 (1963).
2. R. D. Comtois of the National Staphylococcus Phage Typing Reference Center of Canada has just written that UC-18 strains of *S. aureus* are currently causing sepsis in Canadian hospitals.
3. Aided by U.S. Army contract DA-49-193-MD-2455.

22 May 1964

A Cell System in Which Rate and Amount of Protein Synthesis Are Separately Controlled

Abstract. *The mean cross-sectional area of Haversian systems in adult human ribs tends to be constant in the face of sevenfold changes in the rates at which these systems are made. This implies that different mechanisms control the total amount of cellular work in making Haversian systems and the rate at which this work is performed.*

Haversian systems are units (or a form) of bone which are synthesized by specialized cells called osteoblasts. These systems contain both an organic part which is largely collagen and an inorganic mineral portion. The cross sections of Haversian systems are a good measure of the amount of collagen present in them. This is true because these systems have a cylindrical shape and because the amount of collagen in a unit volume of bone (*1*) tends to be constant, namely, 0.11 mg of collagen nitrogen per cubic millimeter of hydrated matrix (*2*). Other things being equal, changes in areas of cross sections of cylindrical structures are representative of changes in volumes. Therefore changes in the amount of collagen (which is a crystalline protein) in Haversian systems can be estimated by measuring changes in cross sections of these systems.

When the antibiotic tetracycline, which is fluorescent, is administered to patients, it is deposited at the place of new bone formation. The rate at which Haversian systems are formed can be found by measuring the thickness of such tetracycline tissue markers—which appear like growth rings in trees—deposited in the skeleton during known periods of time, as well as by measuring the distance between two markers deposited within several weeks of each other (*3*). Since Haversian systems are formed centripetally by the addition of new matrix on the walls of previously prepared tubular holes, the tetracycline markers resemble growth rings when seen in cross section by fluorescence microscopy. The thickness of the rings is a function of the number of days during which the marker is given, as well as of the rate at which layers of new matrix are added.

Measurements were made on 191 cross sections, made by hand grinding on silicon carbide paper under running water, cut from the middle third of the 5th, 6th, or 7th rib taken from 85 subjects (*4*). Of these, 60 subjects (120 sections) were metabolically normal, having died suddenly for various reasons (*5*). The other 25 subjects (71 sections) had diabetes mellitus which was considered to be under good control with insulin or tolbutamide. Of