not have succeeded if I had tried to hide, on which side my own sympathies are found. This does not mean that I am blind toward the merits or ungrateful for the brilliant results of the work of those whose basic philosophy I do not share. I am perfectly aware of the fact that science, in all its different fields, makes progress only by the clash of ideas, which are not all good or all bad, but good only as far as they give inspiration to new experimental attacks. What becomes, in the end, of either of the opposing ideas is rather unimportant. Probably neither of them will survive finally. But while we are working and trying to open new ways of attack on basic problems, it will be helpful to stop occasionally, look at the basic philosophies lying behind our mental procedure when deriving generalizations, and in doing so clarify our own thoughts by analyzing different thoughts sympathetically but also critically. Then it will turn out, after all, that the Queen in the storybook acted under some illusion when she practiced believing a series of impossible things before breakfast—namely, the illusion that anybody could decide what is possible or impossible. But there is at least one thing we can do, which Willard Gibbs expressed in these words: "One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity." Convinced of the correctness of this statement by a great thinker, I have repeatedly prefaced works of mine with the old formulation of the rule of parsimony *"Frustra fit per plura quod fieri potest per pauciora."* This is exactly what I have tried to apply also today. If I have failed I must exclaim with Job: "Is there iniquity in my tongue? Cannot my taste discern perverse things? Teach me, and I will hold my tongue: and cause me to understand where I have erred."

Some Aspects of the Chemistry and Biochemistry of Cholesterol*

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CHOLESTEROL, discovered by Chevreul in 1815 and readily available for experimentation from gallstones or brain, has been the subject of innumerable researches for more than a century, but it still presents certain problems of interest that are under active inquiry. This solid alcohol of the formula $C_{27}H_{45}OH$ is no minor constituent of the animal body. The total quantity of cholesterol in a man weighing 65 kg is approximately 210 g, or 0.3 percent of the wet weight (*1*). The largest amounts are present in the skin (51 g) and nervous tissue (35 g); the tissue concentration varies from 0.14 percent (muscle) to 4.5 percent (adrenal gland). The sterol normally present in plasma to the extent of 0.2 percent is partly free (27 percent) and partly as esters of higher fatty acids, while that present in red blood cells (0.12 percent) and in nervous tissue (1.9 percent) is completely unesterified. The cholesterol of herbivorous animals is derived exclusively by biosynthesis, while that of man is supplied by a combination of biosynthesis and diet. R. P. Cook has demonstrated (*2*) that the intake of 0.58 g of cholesterol per day from an average normal diet (*3*) can be increased to 6.9 g by a regime of menus involving consumption of 20 eggs per day.

What is the role of cholesterol? In what way or ways is it useful to the animal organism? The free cholesterol of nervous tissue appears to serve the function of forming a component of a structural unit of the tissue; Finnean (*4*) has postulated a specific orientation of the molecules of cholesterol and phospholipid in a complex that, in combination with protein, constitutes the structure of myelin. It seems to me likely that the cholesterol in plasma plays a key role in the transport of neutral fat, by the mechanism suggested in the following idealized representation:

$$\text{Lipoprotein A} \begin{cases} \text{protein} \\ \text{phospholipid} \\ \text{cholesterol} \\ \text{glycerides} \end{cases} \underset{+\text{ glycerides}}{\overset{-\text{ glycerides}}{\rightleftharpoons}} \text{lipoprotein B} \begin{cases} \text{protein} \\ \text{phospholipid} \\ \text{cholesterol} \end{cases}$$

The protein may be the cart, and the lipid part of the sterol may supply a lining for reception of the cargo of other lipid. A possible function of the free cholesterol present in high concentration in the membrane of the red blood cell is to form complexes with, and so detoxify, substances that otherwise would have a hemolytic action (*5*). The metabolism of cholesterol is surely associated with that of the steroid sex hormones and cortical hormones, since Bloch (*6*) has demon-

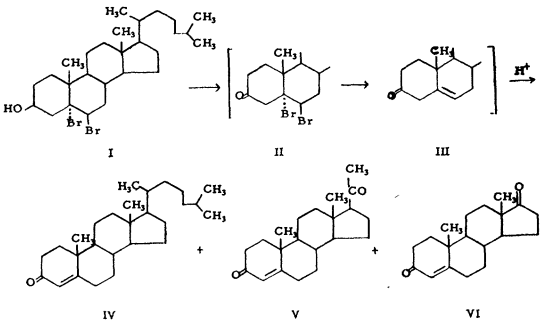
* A lecture delivered in Paris, Nov. 13, 1953, under the auspices of the Societé Chimique de France and the Societé de Chimie Biologique.

strated conversion of cholesterol into pregnanediol, a metabolite or progesterone. It is possible that cholesterol serves as precursor both of these hormones and of vitamin D_3.

Is cholesterol, on occasion, also involved in pathological changes? It is assuredly involved in the formation of gallstones, since these are composed of free cholesterol to the extent of 70 to 80 percent, and in hypercholesteremia, which may be attended with a three- or fourfold increase in blood level. It is involved also in arteriosclerosis, since the sterol content of arteriosclerotic aorta is 5 to 50 times that of normal aorta, but the question of whether or not cholesterol is a causative agent is still uncertain. Myxedema, a disease due to hypofunction of the thyroid gland, is characterized by lowered rate of basal metabolism and augmentation in blood cholesterol. There are some suggestions of an involvement of a spleen sterol in thrombocytopenic purpura (*7*) but the evidence is very tenuous.

The problem that I wish to discuss in particular is that of the possible carcinogenicity of cholesterol, or of some related or derived substance. I became interested in the problem as the result of a conversation in London in June 1950, with Sir Ernest L. Kennaway, who, while on retirement from his post as physiologist at the Chester Beatty Research Institute of the Royal Cancer Hospital, had followed with growing interest the results of a study conducted by his associate, I. Hieger. Hieger had observed (*8*) that subcutaneous injection of cholesterol in lard solution into several hundred mice resulted in 4 to 6 percent incidence of slowly developing (18 mo) tumors at the site of injection. It seemed to me that cholesterol itself, which is so widely distributed in the body, could hardly have the properties of a carcinogen of even low-order potency but that the tumors appearing at the site of the injected material must have been initiated by some transformation product of cholesterol or some unknown companion substance.

I then recalled the extraordinary observation of Bischoff and Rupp (*9*) that injection into mice of a crude commercial progesterone preparation afforded slowly developing tumors in 32 percent of the animals tested, whereas pure progesterone proved to be wholly noncarcinogenic. The crude progesterone preparation was obtained by a method developed by Spielman and Meyer (*10*) that consisted in oxidizing cholesterol dibromide with acidic permanganate in a benzene-water system, followed by debromination with zinc and acetic acid, a process attended with migration of the double bond from the Δ^5-position (III) to the Δ^4-position (IV, V, VI). Extraction of a petroleum ether solution of the reaction mixture from 50 g of cholesterol with concentrated hydrochloric acid removed an oil containing, according to bioassay, 100 mg of progesterone (V). A small amount of androstenedione (VI) was also isolated from this oil, which is the material Bischoff and Rupp had found to be carcinogenic. From the residual material not extracted by acid, Δ^4-cholestene-3-one (IV) was isolated in over 50 percent yield. Pure samples of the two known by-products, IV and VI proved, like progesterone, to be noncarcinogenic.



I II III

IV V VI

The two series of experiments seemed to me to suggest the existence of a nonaromatic, possibly endogenous, steroid carcinogen related to cholesterol. The discovery that the polycyclic aromatic hydrocarbon methylcholanthrene is a highly potent carcinogen (*11*) and that it can be produced in the laboratory, albeit by pyrolytic reactions, from normal constituents of the body—namely, desoxychloric acid (*12*), cholic acid (*13*), and cholesterol (*14*)—suggested the hypothesis that cancer may originate through abnormal metabolism of a sterol or bile acid to an aromatic hydrocarbon such as methylcholanthrene. The estrogenic hormones are probably correctly described as partially aromatized sterol derivatives: estrone, estradiol, and estriol contain one aromatic ring; equilenin contains two. Methylcholanthrene contains four aromatic rings, and a reasonable if wholly speculative pathway for its metabolic formation from adrenal cortical hormones has been suggested (*15*). However, all attempts to demonstrate the *in vivo* conversion of a natural steroid to an aromatic hydrocarbon of the type of methylcholanthrene have failed, and the accumulated evidence of 19 yr of research on the subject strongly discounts the possibility that such a process can be a cause of cancer. However, there is nothing to exclude the possibility that some transformation product of a natural steroid other than an aromatic hydrocarbon is capable of initiating malignant growth. The property of carcinogenicity is now known not to be specific to hydrocarbons of the methylcholanthrene and benzpyrene type but to be exhibited, in varying degree and kind, by such structurally distinct compounds as *o*-aminoazotoluene (*16*), 2-acetylaminofluorene (*17*), and vinylcyclohexene diepoxide (*18*). Carcinogens of still other types may well be possible, including the steroid type that I have postulated. The cholesterol examined by Hieger and the crude progesterone examined by Bischoff and Rupp might conceivably contain some elaborate substance roughly related to vinylcyclohexene diepoxide, but it could hardly contain any nitrogen compounds or any aromatic hydrocarbons. All previous attempts to demonstrate the *in vivo* formation of a carcinogen from a steroid or to detect such a substance in cholesterol, as such or after

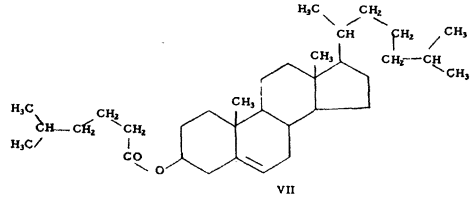
heat treatment or irradiation, have been based on the assumption that the carcinogen is aromatic and have involved searching for something having the spectrographic characteristics of an aromatic compound. I decided to search for a substance still having the chemical characteristics of a sterol or steroid hormone.

My inquiry, begun in the summer of 1950, has led to a succession of alternate hypotheses of varying degree of attractiveness and plausibility. Each has pointed the finger of suspicion at some compound or compounds that have appeared worthy of investigation, and these have been prepared in pure form and supplied to laboratories willing to test them for carcinogenicity in mice. Such a biological assay is a lengthy process. In the two studies cited, the tumors observed appeared only after an induction period of about 18 mo. A compound cannot be declared to be negative until all the mice have died, after perhaps 28 mo, and even then one can say only that the compound is negative under the particular conditions selected. Hence, definitive reports from the cooperating biological laboratories are not yet available for evaluation of any of the hypotheses to be presented.

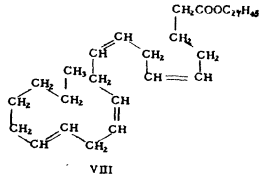
The first idea was suggested to me by the fact that, in their control experiments, Bischoff and Rupp observed no tumor production from cholesterol injected into mice in sesame oil or in colloidal aqueous dispersion, whereas the tumors observed by Hieger resulted from injection of cholesterol in 20 percent solution in lard. The long period of incubation of the implanted cholesterol-lard mixture could afford opportunity for a transesterification that might produce an ester of cholesterol with a fatty acid abnormal to the particular tissues of the injection site. Differences have been noted in the amounts of ester cholesterol and phospholipid in the cell nuclei of normal and tumorous rat livers (*19*), and Leary (*20*) has expressed the view that crystalline ester cholesterol deposited focally is the stimulating agent responsible for the growth of benign cortical adenomas in man.

That the Spielman-Meyer process affords both cholestenone and progesterone shows that the side chain is in part retained and in part subjected to oxidative fission. Since methyl isohexyl ketone is a known product of oxidative fission of the side chain (*21*), isoheptylic acid might have been produced in the oxidation step; the final partition of the reaction mixture between petroleum ether and concentrated hydrochloric acid could have effected esterification of unchanged cholesterol with such an acid. As far as is known, cholesteryl isoheptylate would be abnormal to subcutaneous tissue in respect both to the odd-carbon content and the branching of the fatty acid component (*22*).

Hence, cholesteryl isoheptylate (VII) was synthesized (*23*) and submitted for assay, along with a few other esters, including the arachidonate (VIII). Arachidonic acid seemed of interest as an acid component, since this tetraunsaturated C_{20}-acid is present in the fatty acids of human depot fat to the extent of only 0.6 percent (*24*) but accounts for 22 percent of the fatty acids of the phosphatid fraction of beef adrenal glands (*25*). Also, when the formula is arranged as in VIII, the multiple double bonds would seem to afford invitation for cyclization to a steroid-like structure.



VII

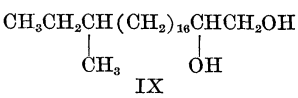


VIII

A second, rather vague idea, was that the suspected steroid carcinogen might be a hitherto unknown or unexplored product of oxidation of cholesterol, possibly a variant of one of the hormone structures. In the search for some unusual oxidation product, I reinvestigated extensively both the partial (*26*) and exhaustive (*27*) oxidation of cholesterol with hexavalent chromium derivatives. The structures of two of the five known oxidation products were elucidated, and three new products were isolated. The main pathway of oxidation was shown to proceed through initial dehydrogenation of cholesterol to Δ^5-cholestene-3-one, represented in the foregoing formulas as the hypothetical intermediate III. A very remarkable product of partial "oxidation" was identified as epicholesterol, a product of rearrangement regarded as resulting from a process of addition-elimination of chromic acid to the double bond. The third new product is a still unidentified substance of the formula $C_{27}H_{44}O_3$ temporarily designated Ketone 104 (*28*), since the first isolation was recorded on page 104 of my notebook (Vol. 23). The substance, formed in only 1 percent yield, was at first (*28*) thought to be derived from a companion substance but has been shown since to be derived from pure cholesterol. It is surely of an unusual structural type, as can be seen from a tentative formulation presented later in this discussion, and it is under assay for carcinogenicity, although there is no reason to suspect that it has any physiological activity or can arise in the body.

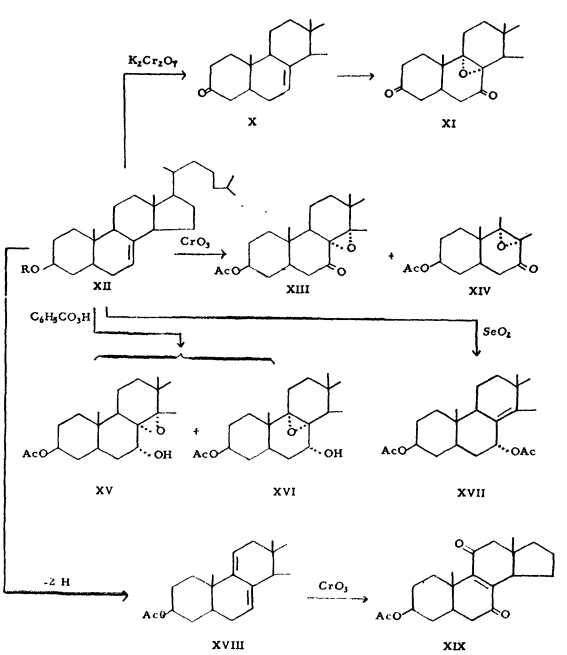
My oxidation experiments had afforded extremely small amounts of other products that I thought could not have come from cholesterol itself, and I was thus led to reinvestigate the question of the homogeneity of sterol extractable from animal tissues. Windaus and Stange (*29*) had isolated the companion 7-dehydrocholesterol (provitamin D_3) by chromatographic fractionation of 2 kg of egg yolk cholesterol containing 0.18 percent of provitamin by spectrophotometric analysis in a series of elutions utilizing more than 1000

liters of solvent. Schoenheimer (*30*) had presented indirect evidence suggesting the presence in cholesterol of the reduction product cholestanol. I established the presence of cholestanol unambiguously by direct isolation (*28*) and isolated as well an isomer of cholesterol characterized as Δ^7-cholestenol (*28*); for material of biological origin, I have suggested the name lathosterol. My coworker, Bidyut K. Bhattacharyya, isolated the further companion cholestane-3β, 5α, 6β-triol (*31*), and the Italian workers Ercoli and de Ruggieri (*32*) have isolated a component designated cerebrosterol and characterized as 24-hydroxycholesterol. In work yet not reported, I have confirmed their isolation of cerebrosterol and have isolated from wool fat (degras) a further substance that my assistant, Wei-Yuan Huang, has characterized as not a sterol but a diol of the probable formula IX. It is related to batyl, chimyl, and selacyl alcohol, which are ethers of the type $ROCH_2CH(OH)CH_2OH$ (*33*).

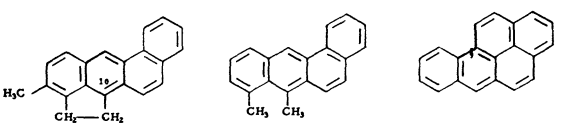


IX

Lathosterol is a regular constituent of tissue sterol, and the amount present is so great (0.5–3 percent) that the substance can hardly be a carcinogen *per se*. It is much more sensitive to oxidation than cholesterol, and hence oxidation under a variety of conditions was investigated to see whether any of the products might have potentialities as possible carcinogens. One striking and unique characteristic of the Δ^7-stenol is that, on oxidation as free alcohol or acetate with hexavalent chromium or with peracids, it affords ketoxides (XI, XIII, XIV) or oxido alcohols (XV, XVI), which bear some resemblance to the carcinogenic epoxides described by Hendry *et al.* (*18*). Study of the reaction



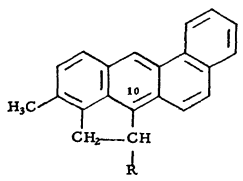
with selenium dioxide in acetic acid (*34*), which proceeds with bond migration to give XVII, was of particular importance in establishment of the configurations of the aforementioned epoxides. Oxidation under very mild conditions with mercuric acetate, bromine, or N-bromosuccinimide effects dehydrogenation to the 7,8,9,11-diene XVIII, which is a type recently studied intensively as a key intermediate for the synthetic production of cortisone from natural sterols. Thus, oxidation of XVIII with a variety of reagents results in introduction of oxygen at C_{11} either as a keto group (XIX) or as an epoxide. The two steps of oxidation proceed so easily as to suggest that the lathosterol present in lard-injected cholesterol may be oxidized by peroxides present in the lard to an 11-oxygenated steroid that might contain one or two epoxide groups. The possible carcinogenicity of such products is under investigation. Since the first step in the Spielman-Meyer process is a bromination, the lathosterol present could have been dehydrogenated to a diene of type XVIII, and the carcinogen could be a product of oxidation of this substance.



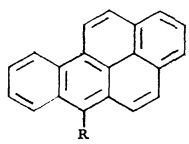
XX XXI XXII

Still another hypothesis, the most recent one, resulted from an entirely different line of reasoning. In the period 1935–43, my research group studied extensively the correlation of carcinogenic activity of aromatic hydrocarbons with structure and with chemical reactivity. By, so to speak, dissecting the methylcholanthrene molecule (XX), we were able to show that some structural features are unimportant, while others make major contributions to carcinogenic potency. Thus, the methyl group can be left off and the five-membered ring opened without loss in activity, since XXI is a potent carcinogen. It is particularly important that the molecule contain a 1,2-benzanthracene ring system with a carbon substituent at the meso position 10. 3,4-benzpyrene (XXII), a second highly potent carcinogen, also has the 1,2-benzanthracene ring system and this possesses a carbon substituent at the meso position 9. We then found that these two potent carcinogens are endowed with remarkable susceptibility to substitutions, manifested in the unique reaction of diazo coupling (*35*), in oxidation by lead tetraacetate at a low temperature (*36*), and in condensation with thiocyanogen (*37*). Under comparable conditions, ordinary aromatic hydrocarbons and less potent carcinogens are inert, and a definite if rough correlation seems to exist between carcinogenic potency and chemical reactivity. Furthermore, the point of attack in the substitutions of methylcholanthrene is at the methylene group at the meso position 10 (XXIII), a center deduced in the other study to be of particular importance to carcinogenic potency. In 3,4-benzpyrene the point of attack is at a position cor-

responding to C_{10} in the 1,2-benzanthracene ring system. In 1941 (*15*), I suggested that production of tumors in animals after injection of these hydrocarbons may be dependent on their special chemical reactivity and may be initiated by interaction of the hydrocarbon with the disulfide link of a proteinoid enzyme, with attachment of the hydrocarbon and liberation of a sulfhydryl group. Although I myself later discounted the concept of a chemical interaction (*38*), a recent review by Wolf (*39*) indicates that it is still entertained by some workers in the field.



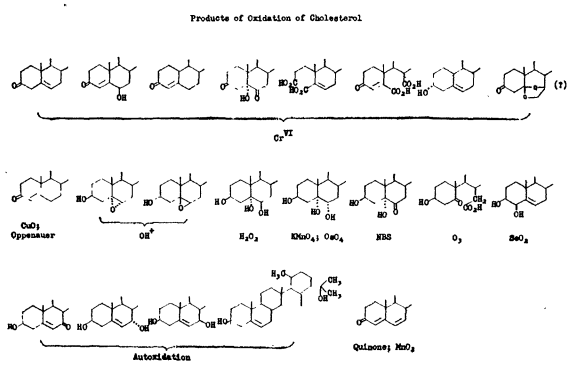
XXIII



XXIV

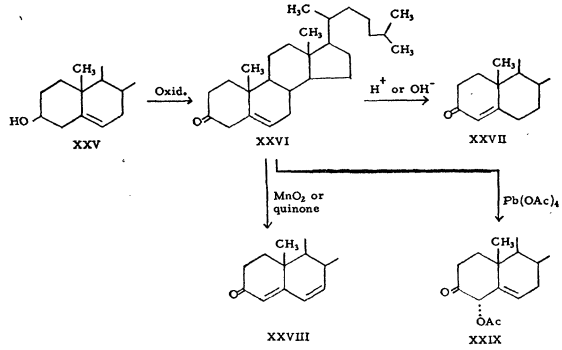
(R = $-N{=}NC_6H_4NO_2$, $-OCOCH_3$, $-SCN$)

Irrespective of the question of the mode of action, the empirical correlation between carcinogenic potency and chemical reactivity seems highly significant. Furthermore, it is remarkable that methylcholanthrene and 3,4-benzpyrene exhibit similar chemical properties, since they really are of two distinct types; in the first, substitution occurs in a methylene group, whereas in the second it occurs in an aromatic ring. It would seem possible that a substance of still a third type having comparable chemical reactivity might exhibit comparable biological actions. Does any companion of cholesterol, or any product of oxidation of the sterol or its companions, possess the distinctive chemical reactivity of methylcholanthrene and 3,4-benzpyrene? Not, I think, any of the known companions or any of ther oxidation products discussed in foregoing paragraphs. The pattern of chemical oxidation of cholesterol itself is extremely complex, since no less than 21 oxidation products are now known having the intact C_{27}-skeleton and resulting from direct oxidation without protection of the double bond. These are indicated in the chart, "Products of oxidation of cholesterol." Attack by dichromate is particularly diversified, since it affords eight products; the last formula in the top line is that tentatively assigned



to Ketone 104. The substances formed by oxidation with other reagents are all well-known products, except 25-hydroxycholesterol, listed as a product of autoxidation. I have found this substance present in commercial cholesterol that had been stored for 4 to 24 yr but not in material freshly manufactured by the same process.

Among these many substances derived from cholesterol by oxidation, there is just one that meets the specifications outlined, namely, Δ^5-cholestene-3-one (XXVI). The methylene group at C_4 is activated by the carbonyl group on one side and the double bond on the other, and it does indeed have the same high degree of sensitivity to substitution as the mesomethylene group of methylcholanthrene and the meso nuclear position of 3,4-benzpyrene. Thus Δ^5-cholestene-3-one is oxidized by lead tetraacetate at 15°C to the 4α-acetoxy derivative XXIX (*40*). It also couples with *p*-nitrobenzenediazonium chloride and absorbs molecular oxygen in boiling benzene, but the products have not yet been characterized. Δ^4-Cholestene-3-one (XXVII), to which the Δ^5-ketone is easily isomerized by acid or base, does not share this reactivity, nor does cholesterol or any of the other products of its oxidation.



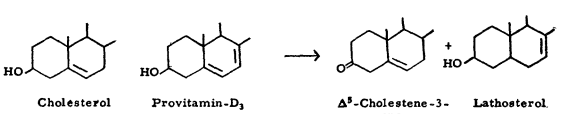
Hence, consideration of the correlation of chemical reactivity and biological potency points to Δ^5-cholestene-3-one as the one substance derived from or related to cholesterol most likely to possess carcinogenic activity. To be sure, the objection may be raised that the correlation is approximate and not precise. Some will go further and point to the alternate concept of Pullman and Pullman (*41*), according to which the factor that determines the potency of hydrocarbon carcinogens and their mode of reaction with enzymes is not chemical reactivity as revealed by substitution reactions but rather the level of electron density at "region K" associated with the phenanthrene double bond, as calculated by wave mechanics. This new theory may well appear more attractive than the one I proposed 12 yr ago, but there is no evidence to exclude the older theory, and in any case it has suggested the experiment of testing Δ^5-cholestene-3-one for carcinogenicity. A negative outcome of the test would not spell a complete victory for the theory of Pullman and Pullman over mine, for any theory must admit of an exception in which some accessory property is

lacking, such as appropriate solubility, absorbability, molecular dimensions, chemical stability, or resistance to metabolic destruction. The theory of Pullman and Pullman is based on a theoretical analysis of aromatic systems and, hence, would not predicate carcinogenicity in Δ^5-cholestene-3-one or any other nonaromatic steroid, but the evidence that such a substance has indeed been responsible for tumors evoked in mice by preparations from cholesterol has seemed to me more convincing than the theoretical argument to the contrary.

Of the various candidate steroids postulated as possible carcinogens Δ^5-cholestene-3-one seems to me the most promising (*42*). It is only 2 hydrogen atoms removed from cholesterol and is the initial product of oxidation with hexavalent chromium, of dehydrogenation with copper oxide, of oxidation with manganese dioxide or by the Oppenauer method. That it has never been isolated from animal tissue is of no great significance, since it is a very labile and reactive substance that one could hope to isolate only by a very special process or as some characteristic transformation product. Saponification or treatment with acids isomerizes the substance to the conjugated ketone XXVII, and such mild agents as manganese dioxide and quinone (in the presence of aluminum alkoxide) oxidize it to $\Delta^{4,6}$-cholestadiene-3-one (XXVIII). Thus, the Δ^4-cholestene-3-one isolated from swine testes (*43*) and the $\Delta^{4,6}$-cholestadiene-3-one isolated from swine spleen (*44*) and from arteriosclerotic aorta (*44*) may have been derived from Δ^5-cholestene-3-one initially present. Lederer *et al.* (*45*) isolated coprostanone from ambergris and inferred that it is a precursor of coprostanol and epicoprostanol, which had been isolated earlier from this source, and that it must have been derived from Δ^5-cholestene-3-one, formed initially by oxidation of cholesterol.

The hypothesis regarding Δ^5-cholestene-3-one does not help much in clearing up the mystery of the carcinogenicity of the Spielman-Meyer progesterone. The crude reaction mixture formed in the debromination step may well have contained considerable Δ^5-ketone as the result of incomplete isomerization, but this probably would have been isomerized fully in the subsequent treatment with hydrochloric acid and surely would not have been extracted by the acid in unaltered form.

Early claims purporting to show that cholesterol acquires carcinogenicity on irradiation with ultraviolet light or on heat treatment (*46*) take on a somewhat different aspect when considered in the light of the present speculations. Thus A. H. Roffo's extensive work on the feeding of irradiated cholesterol to mice (600 test animals, 1000 controls) has been largely discounted, because his claim to have identified polycyclic aromatic hydrocarbons from the irradiated material could not be substantiated by others; but if the carcinogen thought to result from photoxidation were a steroid, it might well have escaped detection, particularly if it were the labile Δ^5-cholestene-3-one. This ketone conceivably can arise by a process other than oxidation—namely, by disproportionation, a reaction often induced by heating. The hydrogen acceptor could be cholesterol itself, which would afford the known companion cholestanol. However, the 5,6-double bond of provitamin-D_3 is more reactive (hydrogenable with Raney nickel) than that of cholesterol and, hence, a more likely process of disproportionation is that formulated:



Cholesterol — Provitamin-D_3 — Δ^5-Cholestene-3-one — Lathosterol

The three alcoholic components are all normal constituents of tissue sterol, which would make the fact of hydrogen exchange all the more likely to be overlooked.

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News and Notes

125th National Meeting of the American Chemical Society

An appeal to America's scientists to strive for greater public understanding of—and support for—free, uncommitted research was made by Louis P. Hammett, head of the Columbia University chemistry department, in an address at the American Chemical Society's 125th national meeting, held in Kansas City, Mar. 23–Apr. 1. The address, marking Columbia's bicentennial, was presented at a general session of the Society. Discussing "Rights and responsibilities in the search for knowledge," Prof. Hammett linked the nation's prospects for survival to the new weapons and other discoveries that may be expected from unprogrammed research in view of the great contributions made by such research in the past. There is no reason to suppose, Prof. Hammett said, that we can keep ahead of our potential enemies indefinitely with respect to programmed and outright developmental research, "particularly if they continue to produce technically trained men faster than we do." He pointed out that the Communist philosophy scornfully rejects exploratory research that has no specific goal, and added: "The fact that our society does admit the value of this kind of research and does support it, although somewhat feebly, is to my mind our best hope for peace and security."

Programmed research also is necessary, Prof. Hammett emphasized, but since its probable benefits are immediately apparent it wins support more easily. If government and industry are to increase their support for uncommitted research, he asserted, they must have the backing of an informed public opinion—and it is up to the scientists, who know the facts better than anyone else, to help the public develop an informed opinion.

Former President Harry S. Truman, who addressed a luncheon of the Division of Chemical Marketing and Economics, predicted that the next half-century would witness scientific developments as yet undreamed of. He expressed the wish that he could again be 20 years of age, instead of almost 70, so that he could see them. Mr. Truman praised scientists for their part in raising the world's living standard and urged them to continue studying the unknown for the benefit of mankind. He stressed the potentialities for world good in atomic energy and voiced the hope that neither the atom bomb nor the hydrogen bomb would ever again have to be used as a weapon.

Identification of a fourth abnormal form of hemoglobin in human red blood cells was among the advances reported in 697 technical papers. Harvey A. Itano of the California Institute of Technology, who received the Eli Lilly and Company Award in Biological Chemistry, announced the new hemoglobin in his award address. He and his colleagues, working under Prof. Linus Pauling, had previously traced the disease called sickle-cell anemia back to a defective hemoglobin and subsequently had identified two other abnormal forms of human hemoglobin. Their successes confirmed Prof. Pauling's theory that sickling—the occurrence of sickle-shaped red corpuscles—might result from an abnormality of the hemoglobin molecule. Prof. Pauling believes that some day such other maladies as heart disease and cancer may prove to be molecular in origin and thus susceptible to entirely new forms of treatment.

Progress in the study of the antibiotic azaserine, which is said to retard the growth of animal cancer, was described in a series of papers by chemists from the Sloan-Kettering Institute for Cancer Research; Parke, Davis and Company, and The Wellcome Research Laboratories. The antibiotic was reported to be particularly effective when used in combination with the compound 6-mercaptopurine. So far, preliminary clinical studies of azaserine in several forms of human cancer have not been impressive, according to C. Chester Stock, chief of Sloan-Kettering's experimental chemotherapy division, but researchers are hopeful that further studies will yield more encouraging results. In any event, he said, azaserine should prove a useful tool in learning more about the way cells grow.

Indications that cancer might be combated successfully through a combination of dietary control and chemotherapy were reported by James B. Allison, professor of physiology and biochemistry in Rutgers University, and associates. Studies now under way at Rutgers show that the life of a tumor-bearing animal may be prolonged through diet control, Prof. Allison said, and this may make it possible to use such chemicals as the triethylenimines to slow up, stop, or even cause regression of the cancer. Administration of T.E.P.A. (triethylenimino phosphoramide) to labora-