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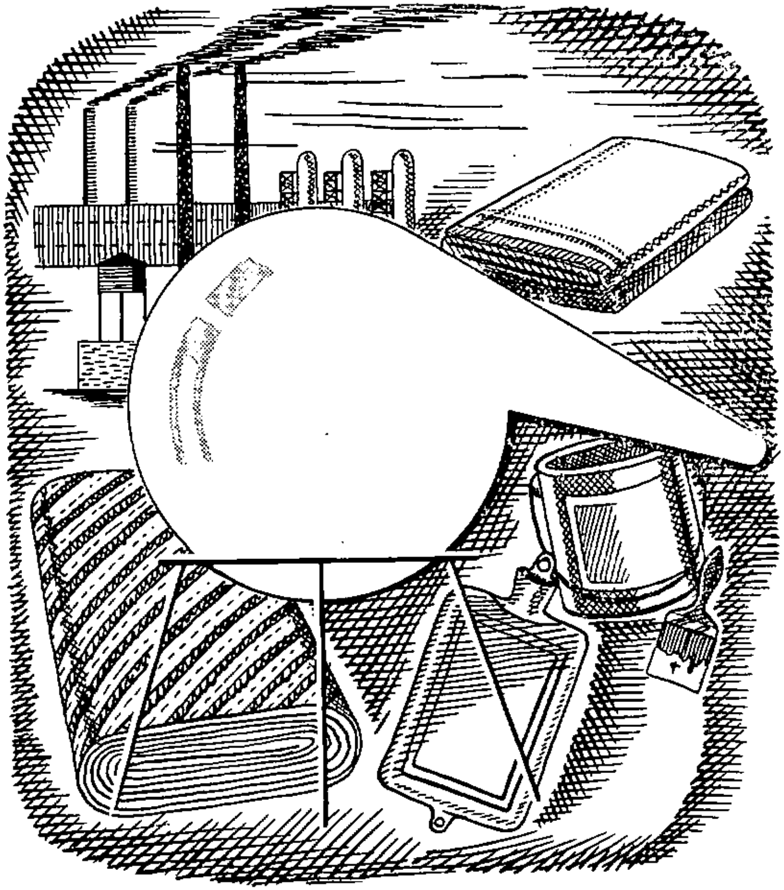


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SOME INSIDIOUS HARMFUL EFFECTS OF ORGANIC CHEMICALS ON MAN.

By George Maxwell Richardson,
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The steady growth of the chemical industry will lead to a continuing search for economic outlets for its products. Clearly some of these outlets will entail a known or accidental exposure of human beings to chemicals which were foreign to their environment until a few decades ago. In persons so exposed, it can be expected that their tissues will deal with the new hazards along lines developed for dealing with the accustomed natural hazards. However, it does not follow that this attempt to counter a new hazard with an old defence will invariably be beneficial.

To the ordinary chemist, as to the general public, the greatest danger from the new chemicals lies in those whose noxious effects are neither immediate nor acute. Acute toxicity can be quickly and surely demonstrated in animal experiments, and knowledge of it soon becomes widespread among potential users. A greater danger follows from the subtle or insidious effects of chemicals which seem at first sight to be innocuous. Recognition of such effects may not occur until long after the first apparently harmless exposure, or even after all exposure has ceased. All too easily, the relation between chemical cause and pathological effect can be blurred over and lost. Indeed, the relation can often be demonstrated with certainty only in susceptible experimental animals.

It is, however, already well established that different animal species may employ different defence mechanisms against harmful chemicals, or, if endowed with alternative defence mechanisms, may use these to different extents. In particular, there are characteristic differences between carnivorous and herbivorous animals. A

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direct result of this is that proof that a given chemical is harmless to a single animal species after prolonged administration cannot be taken as sufficient proof of its harmlessness to man. Conversely, proof that a chemical is harmful to a susceptible species is usually accepted as reason enough for considering it hazardous to man. The argument may not seem wholly valid, but in human affairs allowance has always to be made for idiosyncrasy in individual susceptibility. An outstanding illustration, both of this and of species differences, has been the difficulty met in relating the "spontaneous" degeneration of human blood cells known as agranulocytosis to the ingestion of amidopyrine (pyramidon, p. 69) and other aniline derivatives. In the first place, only a proportion of people using amidopyrine ever developed agranulocytosis, and in the second, extensive experiments in rats, guinea-pigs, rabbits, dogs and monkeys failed to reproduce the condition with any certainty (Climenko, 1936; Kracke, 1938). Yet in Denmark in 1934, the disease virtually disappeared with cessation of imports of the drug, and subsequent clinical experience has established the relation beyond dispute. Similarly, even after detailed studies incriminating naphthylamines as a cause of bladder cancer in the dye industry (Evans, 1937), experimental attempts to reproduce the condition failed until at last the dog was found susceptible to 2–naphthylamine (Hueper *et al.*, 1938; Bonser, 1947; p. 72).

These instances, agranulocytosis and bladder cancer, illustrate the difficulty of relating a known pathology to an unknown chemical cause, but the difficulties of testing a known chemical for an unascertained pathology are no less formidable. This is conveniently illustrated by the pathology of alloxan, the ureide of mesoxalic acid (p. 73). Though the acute toxicity of alloxan by mouth had long been reported (Lusini, 1895; Wiener, 1899), the demonstration by Dunn *et al.* (1943) that on injection it specifically destroyed the *beta* islet cells of the pancreas in rats and rabbits, and, in fact, produced an irreversible diabetes after a single intravenous dose as small as 0.05 g./Kg. in the dog (Goldner & Gomori, 1944) came as a very great surprise.

Undoubtedly, prolonged and exacting studies are required before the harmlessness of a given chemical to man can be asserted on the grounds that no deleterious effect of prolonged administration can be observed in the tissues or on the functions of several, suitably-selected animal species. Certainly, exact knowledge of insidious toxic effects will lag far behind the introduction of new chemicals as public hazards. Of course, one may hope that facilities for making unfettered studies of such hazards will be widely extended in all countries. Yet in the meantime, it may assist chemists who are called upon to assess the importance of these hazards if some review is attempted of the known biochemical and pathological properties of the more important chemical structures.

General Considerations.

It will be appreciated that the field to be covered is immense, and can only be reduced to a reasonable compass by confining attention to the broader generalisations. The most important are, firstly, that relatively few of the chemicals to which we are exposed will gain access to sites susceptible to damage, and, secondly, that a proportion, even of these, will be excreted or otherwise disposed of at a rate to keep their concentration below a critical level. Referring to the former, barriers are imposed by the skin, by the epithelium of mouth, throat, nose and lungs, by the gastro-intestinal *milieu,* the gastro-intestinal epithelium, the blood, the liver, the permeability of tissues, and so forth. Of the membranous barriers, the gastro-intestinal epithelium is readily penetrated by water-soluble chemicals and by fat-soluble chemicals after admixture with bile, but this loophole is carefully guarded by the gastro-intestinal *milieu* before absorption and by the wide detoxifying powers of the liver directly following absorption. Although all chemicals circulating in the blood will eventually be subjected to the influence of the liver, those which gain access by injection, or by penetrating the skin, nose, throat, lungs, mouth, oesophagus, or rectum may reach the liver only after numerous circuits of the body. It therefore follows that chemicals taken by injection, anointment, breathing, sucking, or *per rectum* may act in a manner differing both in effectiveness and quality from that after swallowing. Pharmacological effects and immediate toxicity are usually greater after intravenous injection than after swallowing.

Considering first the skin and epithelial membranes, harmful chemicals may either attack these or penetrate through them (or both). Attack usually produces evident rather than insidious damage, and so need be mentioned only incidentally in this article. It is interesting to note, however, that the sensitiveness of the eyes and nose often protects against over-exposure to irritant chemicals, as, e.g. α–halogenated, and $\alpha:\beta$–unsaturated ketones, which condense with –SH groups and are powerful lachrymators when volatile (Dixon and Needham, 1946; Dixon, 1948). Information about penetration of these membranes has been rather sporadic until recently, but interest in insect repellants should assist in expanding knowledge of percutaneous absorption (Draize *et al.*, 1948; Smyth and Carpenter, 1948). In general, fat-soluble chemicals of low polarity lend themselves most readily to percutaneous absorption. Absorption from mouth, throat, nose, lungs and rectum can be effective with substances of greater polarity, e.g., nitroglycerine, nembutal, etc., but is even more complicated to systematise. Hazards from absorption of noxious gases through the lungs have been recently reviewed in this Journal by King (1950).

Noxious chemicals may be modified in the gastro-intestinal *milieu* through exposure, while warm, to acid and enzymic hydrolysis, reducing conditions, microbial attack, and to various substrates from food with which condensation may occur. Though more precise information would be desirable, the more likely kinds of chemical change should be clear enough. The instance of tartaric acid and the tartrates illustrates the effectiveness of this barrier. These compounds are present in grapes, raisins, and certain vegetables, and are commonly included in baking powders, and used as jellying and flavouring agents in jams, beverages, and in medicine, apparently without harm (Pratt and Swartout, 1933). Yet when the barrier is side-stepped by sub-cutaneous injection into cats or rabbits, they are serious kidney poisons (Rose 1924a; Simpson, 1925). Apparently, they do not easily penetrate the alimentary epithelium and are largely destroyed by the alimentary microflora (Simpson, 1925). Similarly, many irritant and bactericidal substances swallowed (mustard, caraway, spearmint, cinnamon, garlic, etc.) are likely to be detoxicated by condensation with food residues. Thus the quality of the general diet will probably affect the toxicity of ingested chemicals even before alimentary absorption takes place.

The gastro-intestinal epithelium usually excludes non-hydrolysable macro-molecules, and absorbs little or nothing of various heavily-charged ions (e.g., sulphates or tartrates used as laxatives). Through its action in regulating and delaying absorption, it assists detoxification before absorption and spreads any subsequent load on the detoxifying function of the liver and the excretory function of the kidney.

The liver itself is interposed between the small intestine and the general blood circulation and, provided it is well-nourished and endowed with sufficient enzymic and chemical reserves, will promptly modify absorbed chemicals to alter their toxicity or facilitate their excretion. With habitual deficiency of food intake, as in chronic alcoholics and various tropical peoples, the liver is not so well endowed, and may become cirrhotic or (as in Bantu Africans) even cancerous. Though there are other known sites for modification of strange chemicals, the liver remains the most important.

The blood serves as a buffered, neutral medium which is rich in protein. It provides a vehicle for antibodies against such chemicals as can act as haptenes in combination with tissue proteins (Landsteiner *et al.*, 1935, 1938, 1939).

Excretory functions are undertaken by the kidneys, the gall bladder, the skin, and (to a limited extent) the lungs. Since considerable concentration of the initial glomerular filtrate from the blood takes place in the kidneys, these often suffer damage when the general tissues are spared. Harmful chemicals may also be disposed of temporarily in the bones and fat depots. Accumulation of insecticides in animal depot fats is known (Carter *et al.*, 1948, 1950; Bryson *et al.*, 1950), and cancer of the ear wax duct in rats following administration of carcinogenic amines occurs (Bielschowsky, 1947).

The most characteristic of the known chemical modifications effected in the body are:—

(1) Oxidation of many straight-chain compounds to carboxylic acids or CO_2.

(2) Conjugation of tertiary, secondary and some halogenated primary alcohols (in rabbits) with glucuronic acid.

(3) Reduction of ketones to secondary alcohols, excreted after conjugation as above (except acetone, some of which is excreted unchanged).

(4) Conjugation of aromatic carboxyl groups with glycine or glucuronic acid.

(5) Oxidation of aliphatic side-chains in aromatic compounds to carboxylic acids, excreted in conjugation as above.

(6) Oxidative coupling of halogenated aromatic compounds with cysteine, giving mercapturic acids.

(7) Conjugation of phenols with glucuronic or sulphuric acids.

(8) Oxidation of aromatic rings to phenols, excreted in conjugation as above.

(9) De-alkylation of aromatic ethers, if *para* to suitable blocking groups.

(10) Methylation of pyridine– and quinoline–N.

(11) Acetylation of aromatic amines.

Any chemical gaining access to the circulation will be modified along the above lines, because normal tissues, though they may adapt themselves to varying loads, can only make chemical changes which resemble those they have been specialised to make. The mechanisms for these changes are their only resource in dealing with strange chemicals entering their environment, and our next concern, therefore, is to know what harmful potentialities exist in either the mechanisms or the products of these activities.

Harmful Mechanisms.

Dealing with mechanisms first, the oxidation of alcohols to carboxylic acids appears to pass through the aldehydes as expected.

Where this occurs outside the liver, these aldehydes may induce characteristic harmful effects, such as the permanent blindness following ingestion of methyl alcohol (Keeser, 1931). These effects are commonly attributed to condensation of aldehydes with amino-groups in proteins, though this seems a fragile argument in view of stoichiometric relations (Levy and Silberman, 1937; Gulland and Mead, 1935). A more appropriate mechanism, in the author's view, would be condensation with reactive methylene groups (as in keto-acids) with formation of α:β-unsaturated ketones. The reactivity of the latter with enzymic –SH groups (Dixon and Needham, 1946; Dixon, 1948) would account well for the antibiotic and irritant effect of aldehydes, the especial place of formaldehyde, based on the chemical reactivity of vinyl ketones ($CH_2{=}CR\,.\,CO\,.\,R^1$), and its activity in relatively high dilution. Irrespective of mechanisms, however, any considerable exposure to **methyl alcohol, methylamines** (primary, secondary or tertiary), or **methyl esters** of low polarity (e.g., the refrigerant, methyl chloride) constitutes a hazard to be avoided. Aromatic methoxy groups and methylenedioxy-rings (vanilla, cloves, aniseed, nutmeg, beechwood creosote, piperonal, safrole) are stable in mammals and unlikely to be hazardous except in cases such as (9) above.

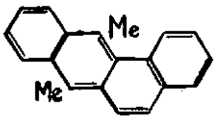
As to higher alcohols and glycols, their aldehyde derivatives do not seem reactive enough to cause untoward results from moderate exposure, with the exception of **allyl alcohol, trimethylene glycol** and **analogous compounds,** and possibly of **ethylene compounds** (dioxan, cellosolves, ethylene glycol, dihydroxyethyl ether, etc., with related amines). The latter are known to cause necrosis of the kidney tubules, particularly in humans, cats and rabbits (Laug *et al.,* 1939), and to lead to fatal uraemia (Schrenk and Yant, 1936). This pathology is difficult to account for on present information, since the ethylene ethers concerned are not oxidised to oxalates by dogs or rabbits (Wiley *et al.,* 1938), and the intermediary carboxylates are not very toxic and appreciably less so than oxalates, e.g., methoxy– and ethoxy–acetates (Militzer and Sallach, 1948); glycollates (Milhorat and Toscani, 1936); diglycollates (Fairley *et al.,* 1936). Intermediary aldehydes may be responsible.

The next mechanisms to be considered are conjugations which involve wastage of essential nutrients. Presumably the body can synthesise an ample supply of glucuronate, and reserves of glycine should also be adequate in mammals, which can synthesise glycine even though a dietary supply assists their growth. There are, however, strict limits to the supply of sulphur compounds for conjugation. These are needed for phenols and halogenated compounds, and an excessive demand on local areas of the liver may lead to enzymes sensitive to iodoacetate, are likely to be affected, and these are the enzymes largely responsible for maintaining haemoglobin in its characteristic ferrous condition (Gibson, 1948). Inactivation of these dehydrogenases will favour an increase of methaemoglobin, by which the E_h within the blood cell and the equilibrium concentration of quinone will be raised. So if the rate of excretion of quinone and the available reserves of –SH are both low, a vicious circle favouring methaemoglobin-formation may be established.

Thus far, only the mature erythrocytes need be affected, but the concomitant raising of the blood quinone level may finally reach a point allowing effective interference with other enzymes. One such mode of interference, as seen in the anti-mitotic action of quinones (Meier and Shär, 1947; Huber, 1947), can be expected to interrupt the supply of immature blood cells and to lead progressively to anaemia, leucopenia, and finally to fatal bacteriaemia as the outcome of agranulocytosis. No evidence has come to notice so far of any abnormal mitoses which have altered the genetic make-up of mammals.

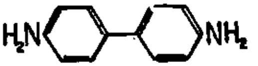
It follows from this hypothesis that the nature of the original substituents will be immaterial to the effect on the blood, provided only that substitution is not too heavy, that the substituents are rather inert metabolically, and that (for preference) they lower the E_0^7 of hydroquinones. Toxic potentialities of an aromatic structure will be reduced by heavy substitution which obstructs the condensation of –SH (as with the natural vitamins of quinonoid structure), or by the presence of sulphonate, carboxylate, straight-chain alkyl, and (in this respect) hydroxyl groups. An instance of the latter effect is the absence of extreme blood changes with **toluene or xylene** in comparison with **benzene**. Toxic potentialities will be enhanced (at equal dosage) by the multiplication of ring systems (of which simple condensed systems lower E_0^7 by 0.17 v. or more, Evans, Gergely and de Heer, 1949), by the presence of unsubstituted or substituted amino-groups (of which the first lowers E_0^7 by 0.18 to 0.25 v., Fieser and Fieser, 1935), by the presence of alkoxy groups (one of which lowers E_0^7 by 0.13 v., Fieser and Fieser, 1935), and possibly by secondary and tertiary alkyl groups (for which no figure has been found).

By the cumulation of appropriate substituents, E_0^7 values should be lowered below the E_h of aerobic tissues, and in that case the oxidised metabolite could be present as a quinone even in metabolising cells. This probability gives point to the knowledge that carcinogenic potentialities (which seem related to growth inhibition, Haddow, 1947) rarely develop in aromatic hydrocarbons which have fewer than four condensed rings (thus, 9:10–dimethyl–1:2–benzanthracene and 3:4–benzpyrene are potent carcinogens), whereas aromatic amines begin to develop these potentialities in much simpler structures (Haddow and Kon, 1947), and even in benzidine (Spitz *et al.*, 1950) and dulcin (Fitzhugh and Nelson, 1950). Moreover, as noted by Wilson *et al.* (1941), Bielschowsky (1947) and others, activity in polycyclic amines with condensed rings is confined to those substituted in position 2, e.g., 2–naphthylamine, 2–aminofluorene, etc. With such substitution, an amino–p–quinone of low E_0^7 is a reasonable product of metabolism, whereas substitution in position 1 would lead rather to a p–quinoneimine of much higher E_0^7. The scope of the above hypothesis may include derivatives of phenanthrene–9:10–quinone, which also has anti-mitotic activity (Lehmann and Andres, 1948), but even so it cannot yet be pressed too far. This is because of the strange specificity apparent in the carcinogenic power of the substituted aminoazobenzenes (Kirby, 1945; Crabtree, 1949). This is quite unaccountable unless the E_0^7 of benzene–azo–hydroquinone is influenced by substituents on the benzene ring to a much greater extent than seems likely in the absence of exact figures. In summary, then, the hypothesis that aromatic compounds become noxious to the body after biological oxidation to substituted quinones provides a generalisation which covers most, but not all, of the accumulated facts. It does stimulate a multitude of questions, including enquiry as to whether any chemical factors may influence the site of carcinogenesis, which only future research can answer.

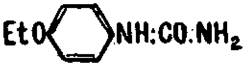


9:10-DIMETHYL-1:2-BENZANTHRACENE

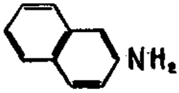
3:4-BENZPYRENE



BENZIDINE

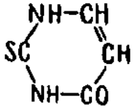


DULCIN

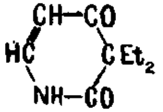


2-NAPHTHYLAMINE

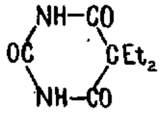
Although the majority of recorded cases of agranulocytosis have followed the administration of aromatic compounds, antimitotic activity is possessed by a much wider group of chemicals than the quinones. This group includes (Dustin, 1947) simple nitrogenous compounds like cyanates, thiocyanates, urethane and thiourea, chlorinated compounds such as the mustard gases and gammexane (Carpentier and Fromageot, 1950), dithioglycerol (British anti-lewisite), trypaflavine, and organic arsenicals, as well as many alkenones (α:β–unsaturated ketones) of which quinones are a special instance of the *cis*-isomer. It is not certain which of these substances can penetrate the body defences well enough to be hazardous, but evidence implicating ingested **thiocyanates** (Lindberg *et al.*, 1941) and **thiourea** (Goldsmith *et al.*, 1944) as blood poisons has appeared, and ingested **urethane** induces lung cancer in mice (not guinea pigs or fowls; Cowen, 1950). Among substances with a *cis*-alkenone linkage, **amidopyrine** (a masked alkenone as well as an aniline derivative; p. 69), was the reputed cause of much agranulocytosis, as also is **thiouracil** (Morton, 1947), while the use of **persedon** (presidon) was soon followed by a fatal case (Covner and Halpern, 1950). This new hypnotic differed only by its *cis*-alkenone structure from such a well-tried barbiturate as barbitone (veronal).



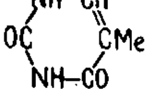
THIOURACIL



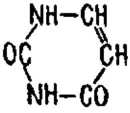
PERSEDON



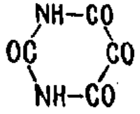
BARBITONE



THYMINE



URACIL



ALLOXAN

The seemingly striking influence of the *cis*-alkenone structure contrasts pointedly with its occurrence, quite harmlessly, in uracil, thymine and guanine. This anomaly might possibly be explained in terms of keto-enol tautomerism, but a more inviting view is that the accident of a similar structure permits a *cis*-alkenone to block some vital biochemical process requiring uracil, thymine, or guanine. This effect can then be grouped with that of the simple nitrogen compounds (possibly including dulcin), since the latter are evident precursors of structures resembling the amidine group of cytosine and adenine (R. $C(=NR^1-)$ NH_2). Since interference with cytosine, uracil, thymine, adenine or guanine could scarcely be without influence on the supply of nucleoprotein for cell division, the characteristic anti-mitotic action reported would seem quite reasonable. These suppositions likewise stimulate many questions which only future research can answer.

Finally, two other examples of toxicity for which the mechanism is obscure warrant brief reference. The first is the **alloxan** diabetes referred to in the introduction. As far as investigation has gone, the effect is specific to alloxan, its reduction products and its mono- (but not di-) N-alkyl derivatives (Brückmann and Wertheimer, 1947). The second is the permanent paralysis induced by **tricresyl phoshate** consumed as an adulterant in Jamaica ginger, parsley oil, salad dressing, etc. (Aring, 1942). Mono- and di- cresyl phosphates are without this effect (Smith, 1934), possibly owing to hydrolysis or to better excretion.

Harmful Results of Disturbance of Function.

Noxious effects following disturbance of physiological functions may be manifold, but are commonly self-evident. It is fortunate that a degree of specificity in chemical structure is the rule, since the effective dose can be extremely small. This is well illustrated by the recent spectacular instances of the alkyl fluorophosphonates and pyrophosphates, of which the fatal dose is less than 100 mg. Four examples of a more insidious type can be selected to show how diverse and important the results of physiological disturbance may be.

The first is the historical disease of ergotism, or St. Anthony's fire. The gangrenous form of this disease is probably to be attributed simply to the action of one of the **ergot** alkaloids in constricting the arterioles of the blood circulation. This is succeeded by a conglomeration of blood clots, loss of circulation in the extremities and the agonising death of the affected tissues, which eventually slough away if severely involved.

The second example follows from the action of certain **4.4^1–bishydroxyphenyl alkenes or alkanes.** These act, apparently through steric similarity with natural oestrogens, as their synthetic equivalents (Dodds *et al.*, 1944). They may lead to reversible effects simulating castration in man, delaying menstruation in women, and suppressing lactation in nursing mothers, so that ingestion from an unsuspected source (e.g., as an anti-oxidant in fats) could initiate important psychological difficulties in either sex.

enzymes sensitive to iodoacetate, are likely to be affected, and these are the enzymes largely responsible for maintaining haemoglobin in its characteristic ferrous condition (Gibson, 1948). Inactivation of these dehydrogenases will favour an increase of methaemoglobin, by which the E_h within the blood cell and the equilibrium concentration of quinone will be raised. So if the rate of excretion of quinone and the available reserves of –SH are both low, a vicious circle favouring methaemoglobin-formation may be established.

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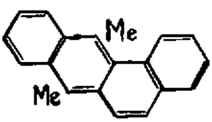

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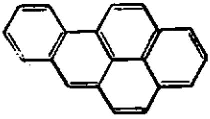
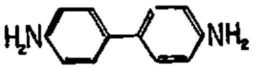
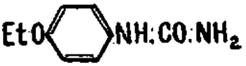


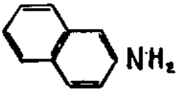
3:4-BENZPYRENE



BENZIDINE

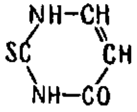


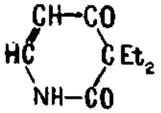
DULCIN

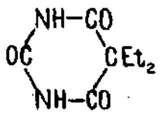


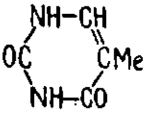
2-NAPHTHYLAMINE

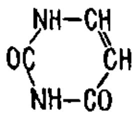
Although the majority of recorded cases of agranulocytosis have followed the administration of aromatic compounds, antimitotic activity is possessed by a much wider group of chemicals than the quinones. This group includes (Dustin, 1947) simple nitrogenous compounds like cyanates, thiocyanates, urethane and thiourea, chlorinated compounds such as the mustard gases and gammexane (Carpentier and Fromageot, 1950), dithioglycerol (British anti-lewisite), trypaflavine, and organic arsenicals, as well as many alkenones ($\alpha:\beta$–unsaturated ketones) of which quinones are a special instance of the *cis*-isomer. It is not certain which of these substances can penetrate the body defences well enough to be hazardous, but evidence implicating ingested **thiocyanates** (Lindberg *et al.*, 1941) and **thiourea** (Goldsmith *et al.*, 1944) as blood poisons has appeared, and ingested **urethane** induces lung cancer in mice (not guinea pigs or fowls; Cowen, 1950). Among substances with a *cis*-alkenone linkage, **amidopyrine** (a masked alkenone as well as an aniline derivative; p. 69), was the reputed cause of much agranulocytosis, as also is **thiouracil** (Morton, 1947), while the use of **persedon** (presidon) was soon followed by a fatal case (Covner and Halpern, 1950). This new hypnotic differed only by its *cis*-alkenone structure from such a well-tried barbiturate as barbitone (veronal).

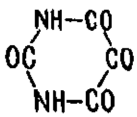

THIOURACIL


PERSEDON


BARBITONE


THYMINE


URACIL


ALLOXAN

The seemingly striking influence of the *cis*-alkenone structure contrasts pointedly with its occurrence, quite harmlessly, in uracil, thymine and guanine. This anomaly might possibly be explained in terms of keto-enol tautomerism, but a more inviting view is that the accident of a similar structure permits a *cis*-alkenone to block some vital biochemical process requiring uracil, thymine, or guanine. This effect can then be grouped with that of the simple nitrogen compounds (possibly including dulcin), since the latter are evident precursors of structures resembling the amidine group of cytosine and adenine (R. C(=NR^1–) NH$_2$). Since interference with cytosine, uracil, thymine, adenine or guanine could scarcely be without influence on the supply of nucleoprotein for cell division, the characteristic anti-mitotic action reported would seem quite reasonable. These suppositions likewise stimulate many questions which only future research can answer.

Finally, two other examples of toxicity for which the mechanism is obscure warrant brief reference. The first is the **alloxan** diabetes referred to in the introduction. As far as investigation has gone, the effect is specific to alloxan, its reduction products and its mono- (but not di-) N-alkyl derivatives (Brückmann and Wertheimer, 1947). The second is the permanent paralysis induced by **tricresyl phoshate** consumed as an adulterant in Jamaica ginger, parsley oil, salad dressing, etc. (Aring, 1942). Mono- and di- cresyl phosphates are without this effect (Smith, 1934), possibly owing to hydrolysis or to better excretion.

Harmful Results of Disturbance of Function.

Noxious effects following disturbance of physiological functions may be manifold, but are commonly self-evident. It is fortunate that a degree of specificity in chemical structure is the rule, since the effective dose can be extremely small. This is well illustrated by the recent spectacular instances of the alkyl fluorophosphonates and pyrophosphates, of which the fatal dose is less than 100 mg. Four examples of a more insidious type can be selected to show how diverse and important the results of physiological disturbance may be.

The first is the historical disease of ergotism, or St. Anthony's fire. The gangrenous form of this disease is probably to be attributed simply to the action of one of the **ergot** alkaloids in constricting the arterioles of the blood circulation. This is succeeded by a conglomeration of blood clots, loss of circulation in the extremities and the agonising death of the affected tissues, which eventually slough away if severely involved.

The second example follows from the action of certain **4.4^1–bishydroxyphenyl alkenes or alkanes.** These act, apparently through steric similarity with natural oestrogens, as their synthetic equivalents (Dodds *et al.*, 1944). They may lead to reversible effects simulating castration in man, delaying menstruation in women, and suppressing lactation in nursing mothers, so that ingestion from an unsuspected source (e.g., as an anti-oxidant in fats) could initiate important psychological difficulties in either sex.

The third example is the unco-ordinated activity of dogs after feeding on **agene-treated flour.** This effect, also reversible, is apparently due to prolonged ingestion of methionine sulphoximine ($CH_3.SONH.CH_2.CH_2.CHNH_2.COOH$) (Bentley *et al.*, 1951), which results from the treatment of flour proteins with agene (NCl_3).

The fourth example is the suggestion (Frazer, 1951) that substances delaying gastro-intestinal digestion and absorption may assist the passage of fermentable food material to the lower small intestine. In this site, an abundant bacterial growth could develop, competing with the host for essential food factors and vitamins, and simulating most features of the peculiar syndrome of sprue.

Concluding Note.

This preliminary survey of a very wide field is inevitably greatly condensed. It passes lightly over very involved topics, and adopts generalisations to which some exceptions are known to the author and others doubtless unknown. It is, nevertheless, hoped that it will provide practical chemists with some guide to the less obvious, though known, harmful potentialities of the organic chemicals they handle. To correct deficiencies in the treatment of special topics key references are usually provided. At the same time, the author hopes to treat these topics more fully in later articles, as opportunity occurs to explore each field in greater detail. He is most grateful to Dr. Muriel Bell for the stimulus of her active interest in this study, and to all his colleagues for enlightening discussions.

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BOOKS RECEIVED.

ULTRAVIOLET SPECTRA OF AROMATIC COMPOUNDS. Robert A. Friedel and Milton Orchin. (John Wiley & Sons Inc., New York.) $10.00.

Strictly, this book is mis-named, as it gives the U.V. absorption spectra of 579 aromatic compounds of certain classes rather than an attempt at covering the complete field of aromatic compounds, as the title implies. The spectra, which give log. of molar extinction coefficient (concentration in g. moles per litre) against wavelength in angstroms, are fairly systematically grouped according to the number of aromatic ring systems in the compound. The work is well documented and references are given to collections of U.V. spectra of classes of compounds not dealt with. The absorption curves are printed on one side of the page only and are arranged so they can be detached and inserted into a conventional three-ring binder. Brief introductory chapters give a résumé of experimental procedure, the use of U.V. spectra in qualitative and quantitative analysis and instruction on the use of the catalogue. The quality of the paper and printing is excellent.

H.B.

THE TRAINING OF CHEMISTS.

The following account of the March meeting of the Auckland Branch has been taken from the minutes. We are indebted to Mr. I. S. Hunt for this concise account. The four speakers represented Government, Industry and the University.

Mr. K. M. Griffin described his personal experience of graduating as a part-time student, while having the opportunity of practising chemistry at the same time. He welcomed the action of Dr. Richardson at the Hamilton Conference in raising the question of the part-time student. He expressed his regrets that the part-time student was now discouraged rather than encouraged as the ideal in training chemists. Mr. Griffin pointed out that the Institute required practical experience before admission to a body of practising chemists, that similar requirements existed for medical and engineering degrees, but no practical experience was required for a science degree. He considered the time was ripe for the Institute to take over the examining of students as is done by the Royal Institute. He supported a recent suggestion that the Auckland Faculty of Science be separated from the rest of the College, and be formed into a separate College of Science located at some country centre, and suggested that the way would then be opened for a new Auckland College of Science. Though it may have to be called an Institute of Technology to prevent clashing with the University College, it could in fact become a live centre for practising scientists and so train our members for the Profession of Chemistry.

Prof. F. J. Llewellyn discussed the ideals of the University, and quoted several eminent authorities. Dr. Beeby in May, 1951, described the traditional task of the University as the conduct of research and the education of a select élite. The Hon. Sir David Smith, Chancellor of the University of New Zealand, in August, 1951, expressed his opinion that the primary object of the University was to make the best provision for the education of the ablest students. Prof. Llewellyn pointed out that these ideals were in general accord with the nineteenth century conception of the University before the impact of technological advance was felt. In those times it was concerned with learning for learning's sake, taking no cognisance of church or state, of commerce or industry. While supporting these principles, the speaker pointed out that the present-day University is dependent on the state for finance and therefore has a reciprocal obligation to the taxpayer. It is also now drawing its students from all classes of society and from a much wider range of adolescent abilities. The speaker went on to compare University structure in Europe, Britain and America.

The third example is the unco-ordinated activity of dogs after feeding on **agene-treated flour.** This effect, also reversible, is apparently due to prolonged ingestion of methionine sulphoximine ($CH_3.SONH.CH_2.CH_2.CHNH_2.COOH$) (Bentley *et al.*, 1951), which results from the treatment of flour proteins with agene (NCl_3).

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◆

BOOKS RECEIVED.

ULTRAVIOLET SPECTRA OF AROMATIC COMPOUNDS. Robert A. Friedel and Milton Orchin. (John Wiley & Sons Inc., New York.) $10.00.

Strictly, this book is mis-named, as it gives the U.V. absorption spectra of 579 aromatic compounds of certain classes rather than an attempt at covering the complete field of aromatic compounds, as the title implies. The spectra, which give log. of molar extinction coefficient (concentration in g. moles per litre) against wavelength in angstroms, are fairly systematically grouped according to the number of aromatic ring systems in the compound. The work is well documented and references are given to collections of U.V. spectra of classes of compounds not dealt with. The absorption curves are printed on one side of the page only and are arranged so they can be detached and inserted into a conventional three-ring binder. Brief introductory chapters give a résumé of experimental procedure, the use of U.V. spectra in qualitative and quantitative analysis and instruction on the use of the catalogue. The quality of the paper and printing is excellent.

H.B.

THE TRAINING OF CHEMISTS.

The following account of the March meeting of the Auckland Branch has been taken from the minutes. We are indebted to Mr. I. S. Hunt for this concise account. The four speakers represented Government, Industry and the University.

Mr. K. M. Griffin described his personal experience of graduating as a part-time student, while having the opportunity of practising chemistry at the same time. He welcomed the action of Dr. Richardson at the Hamilton Conference in raising the question of the part-time student. He expressed his regrets that the part-time student was now discouraged rather than encouraged as the ideal in training chemists. Mr. Griffin pointed out that the Institute required practical experience before admission to a body of practising chemists, that similar requirements existed for medical and engineering degrees, but no practical experience was required for a science degree. He considered the time was ripe for the Institute to take over the examining of students as is done by the Royal Institute. He supported a recent suggestion that the Auckland Faculty of Science be separated from the rest of the College, and be formed into a separate College of Science located at some country centre, and suggested that the way would then be opened for a new Auckland College of Science. Though it may have to be called an Institute of Technology to prevent clashing with the University College, it could in fact become a live centre for practising scientists and so train our members for the Profession of Chemistry.

Prof. F. J. Llewellyn discussed the ideals of the University, and quoted several eminent authorities. Dr. Beeby in May, 1951, described the traditional task of the University as the conduct of research and the education of a select élite. ' The Hon. Sir David Smith, Chancellor of the University of New Zealand, in August, 1951, expressed his opinion that the primary object of the University was to make the best provision for the education of the ablest students. Prof. Llewellyn pointed out that these ideals were in general accord with the nineteenth century conception of the University before the impact of technological advance was felt. In those times it was concerned with learning for learning's sake, taking no cognisance of church or state, of commerce or industry. While supporting these principles, the speaker pointed out that the present-day University is dependent on the state for finance and therefore has a reciprocal obligation to the taxpayer. It is also now drawing its students from all classes of society and from a much wider range of adolescent abilities. The speaker went on to compare University structure in Europe, Britain and America.

THE NEW ZEALAND INSTITUTE OF CHEMISTRY (INC.).

Balance Sheet as at 31st October, 1951.

1950. £		£ s. d.	£ s. d.
69	SUBSCRIPTIONS PAID IN ADVANCE		91 10 4
4	JOURNAL SUBSCRIPTIONS PAID IN ADVANCE		2 12 6
3	SUNDRY CREDITORS		212 7 2
30	PROVISION FOR ESSAY PRIZE		30 0 0
44	TRAVELLING EXPENSES RESERVE		—
	ACCUMULATED FUNDS:		
	Balance 31st October, 1950	848 0 11	
	Less Transfer to Trust Fund	50 0 0	
		798 0 11	
	Add Excess of Income over Expenditure for the Year	38 5 6	
848	Balance 31st October, 1951		836 6 5
452	TRUST FUND		513 18 6
£1,450			£1,686 14 11

1950. £		£ s. d.	£ s. d.
	TYPEWRITERS—		
	Balance 31st October, 1950	8 0 0	
	Add Typewriter Purchased	37 12 0	
		45 12 0	
8	*Less* Depreciation for Year	4 12 0	41 0 0
	ADDRESSOGRAPH PLATES—		
	Balance 31st October, 1950	13 0 0	
13	*Less* Depreciation for Year	2 0 0	11 0 0
	SUBSCRIPTIONS OVERDUE—		
	2 for the year ended 31/10/49	3 3 0	
	9 for the year ended 31/10/50	14 19 0	
	53 for the year ended 31/10/51	81 0 0	
		99 2 0	
61	*Less* Amount Reserved	20 0 0	79 2 0
60	SUNDRY DEBTORS		78 17 7
	NATIONAL SAVINGS A/C. (due 1/7/52)	500 0 0	
505	*Add* Interest Accrued	20 0 0	520 0 0
	CASH BALANCES—		
200	Bank of New Zealand	279 9 4	
143	Post Office Savings Bank	146 5 8	
8	Petty Cash on Hand	17 1 10	442 16 10
	TRUST FUND INVESTMENT—		
452	Post Office Savings Bank		513 18 6
£1,450			£1,686 14 11

W. G. HUGHSON,
Hon. General Secretary-Treasurer.

THE NEW ZEALAND INSTITUTE OF CHEMISTRY (INC.).

Income and Expenditure Account for the Year Ended 31st October, 1951.

EXPENDITURE.

1950. £		£	s.	d.	£	s.	d.
	To Administration & Sundry Expenses—						
3	Audit Fee	3	3	0			
4	Branch Expenses Allowances	6	0	0			
3	Depreciation	6	12	0			
26	Honorarium—Secretary	26	5	0			
7	Legal Expenses	—					
23	Postages and Sundries	30	12	6			
83	Printing and Stationery	39	17	1			
125	Salary—Registrar	145	0	0			
40	Typewriting, Duplicating and Addressing	60	15	11			
69	Travelling Expenses	62	8	0			
—	Expenses re Selection of Younger Chemists under American Chemical Society Scheme	17	9	6	398	3	0
	,, Institute Journal—						
289	Printing, Blocks, etc.	382	7	4			
26	Postages and Sundries	15	15	6			
11	Honorarium—Editor	10	10	0	408	12	10
	,, Chemists' Employment Committee—						
7	Duplicating and Sundries				6	17	0
	,, Examinations Committee—						
9	Duplicating and Sundries				7	18	5
	,, Institute Prize—						
15	Provision for Essay Prize				—		
—	,, Travelling Expenses— Special Allowance to Hon. Gen. Secretary in respect of his visit to America				50	0	0
138	,, Excess of Income over Expenditure for Year Transferred to Accumulated Funds				38	5	6
£878					£909	16	9

INCOME.

1950. £		£	s.	d.	£	s.	d.
607	By Subscriptions				639	8	0
	,, Interest—						
10	Post Office Savings Bank	3	10	9			
5	National Savings Account	15	0	0	18	10	9
	,, Institute Journal—						
20	Subscriptions	24	17	3			
196	Advertising	153	4	7	178	1	10
	,, Chemists' Employment Committee—						
7	Subscriptions				9	0	0
	,, Examinations Committee—						
19	Entry Fees and Sundries				14	12	0
	,, Conference Committee—						
	Surplus of Receipts over Payments	7	18	5			
14	*Less* Share R.I.C. (N.Z. Section)	1	11	8	6	6	9
—	,, Travelling Expenses Reserve— Reserve set up in previous year now closed				43	17	5
£878					£909	16	9

TRUST FUND for the Year Ended 31st October, 1951.

	£	s.	d.		£	s.	d.
To Balance Carried Down	513	18	6	By Balance 31st October, 1950	451	18	6
				.. Transfer from General Funds	50	0	0
				.. Interest on Deposit	12	0	0
	£513	18	6		£513	18	6
				By Balance 31st October, 1951	£513	18	6

AUDITORS' CERTIFICATE.

We have audited the books of the New Zealand Institute of Chemistry (Inc.) for the year ended 31st October, 1951, and have compared them with the vouchers produced to us, and with the above Balance Sheet and accompanying Statements. We have verified the various cash balances, and certify that, in our opinion, the above Balance Sheet shows the true position of the Institute.

DYMOCK, MacSHANE & SCLANDERS,

W. B. MACMORRAN,

Auditors.

Wellington, N.Z., 25th March, 1952.

BOOKS RECEIVED

DIE CHEMISCHE AFFINITÄT. Egon Wiberg, Professor of Inorganic Chemistry in the University of Munich. 254 pages; price 24 D.M. (Walter de Gruyter & Co., Berlin, 1951.)

Primarily a manual to enable the chemist to decide whether a projected reaction is likely to proceed and the probable conditions of temperature and pressure required, this book is based on the present-day less popular utilisation of thermodynamic cycles. It is obviously inspired by the work of G. N. Lewis and M. Randall. Prof. Wiberg begins his preface with the oft-quoted example of the calculation by Lewis of the feasibility of the projected fixation of nitrogen by the reaction

$$N_2 + 2H_2O = NH_4^+ + NO_2^- \quad .$$

This calculation, which according to one version known to the reviewer, enabled Lewis to save a firm inspired by the success of the Haber process, the cost of a huge research project by calculating from his tables of free energy (on the back of an old envelope) that even with the right catalyst the reaction would produce only an infinitesimal concentration of ammonium nitrite, using a fantastically high pressure of nitrogen.

Although the book is rather inadequate as far as its theoretical treatment is concerned, its many excellent examples will enable the chemist to make use of its most important section—its 34-page appendix giving tables of functions which enable the calculation of the affinities of a large number of inorganic chemical reactions. Arranged systematically, the following information is given:—Standard free energy of formation, standard electrode potential, redox potential, chemical potential and standard hydrogen ion exponent of acidic compounds. The book is well printed and appears to be up-to-date in its sources of information. H.B.

THE STRUCTURE OF PHYSICAL CHEMISTRY.—C. N. Hinshelwood, Professor of Chemistry in the University of Oxford. (Oxford. The Clarendon Press, 1951.) 476 pages. Price 35/-.

This is a brilliantly-written book which should be read by all chemists, including those who are interested in obtaining only a general picture of Physical Chemistry, without delving too deeply into its details. It starts from first principles and its very minimum of mathematical treatment can be followed readily by most. Each chapter is preceded by a synopsis. It seems strange, considering the importance of electrochemistry as an integral unit of Physical Chemistry, that it should be summarily dismissed in a few pages, no mention being made of electrode potentials, whereas the kinetics of bacterial cells, a topic bordering on biochemistry, should receive fairly detailed consideration. Notwithstanding this lack of balance, this book is an invaluable contribution to chemical literature. Its sections are as follows: (1) The world as a molecular chaos. (2) Control of the chaos by the quantum laws. (3) The electrical basis of matter. (4) Forces. (5) The forms of matter in equilibrium. (6) Passage towards equilibrium. The quality of the paper and printing is excellent and the index is adequate.

H.B.

PHASE TRANSFORMATIONS IN SOLIDS. Edited by R. Smoluchowski, J. E. Mayer and W. A. Weyl. (John Wiley & Sons Inc., New York; Chapman & Hall Ltd., London, 1951.) 660 pages; price $9.50.

A symposium on various topics connected with the solid state. The book is of interest mainly to research workers in the field. H.B.

RADIOACTIVITY APPLIED TO CHEMISTRY.—Edited by Arthur C. Wahl and Norman A. Bonner. (John Wiley & Sons Ltd., New York, 1951.) $7.50.

This book, written by twelve leading workers in the field of radiochemistry, is an authoritative statement of the present position of knowledge concerning the use of radio-active isotopes in elucidating chemical problems.

The work is in two parts: the first ten chapters deal with the physical and chemical principles involved in use of radio active tracers, while the remaining 200 pages are devoted to tables giving detailed data concerning exchange reactions, kinetic studies, diffusion, analytical techniques, coprecipitation, oxidation and reduction of carrier-free tracers, surface determination and other related topics.

The first part of the book begins with a full discussion of exchange reaction theory. Then follow chapters discussing applicability of tracer methods to kinetic studies, structural chemistry, diffusion, analytical chemistry, carrier-free materials, new elements, surface chemistry and emanation methods.

The book makes an admirable reference work for the radiochemical research worker. Its value in this respect is enhanced by its completeness: reports on all applications of radioactivity to chemistry published by January, 1950, have been included. This fact alone makes the work eminently worthwhile. A.L.O.

NEWS AND NOTES.

We much regret that several lines in our report on Mr. C. L. Carter in our last issue were transposed through a printing error. The correct report should have read: "Mr. C. L. Carter will be well known to members, being a foundation member and now a Fellow of the Institute. He is also an Associate of the Royal Institute of Chemistry. This is the second occasion he has been elected Chairman of the Otago Branch, and he has also served as its Secretary for eight years. He joined the staff of the Chemistry Department, University of Otago, in 1919, and his interests lie mainly in the field of natural products, his latest contribution being a paper on the chemical constitution of karakin. In 1949 Mr. Carter was granted refresher leave to study for four months at the University of Edinburgh under Prof. E. L. Hirst. . . . ."

In his Chairman's address to the Otago Branch on the 23rd April, Mr. C. L. Carter discussed "Petroleum as a Source of Organic Chemicals." He outlined the phenomenal progress made by oil companies in Britain and the United States over the past 15-20 years in organic syntheses, starting from simple paraffins and olefins. Raw material for organic syntheses was formerly obtained mainly from fermentation processes, now largely superseded.

Industrial cracking of the higher paraffin yields some 6 per cent. of C_1–C_5 gases, and these form the basis of a very large number of important syntheses. Mr. Carter discussed in detail the methods used, and some reaction mechanisms. Such processes as controlled oxidation, catalytic hydrogenation, chlorination, sulphonation, etc., yield an amazing range of chemicals, including alcohols, aldehydes, ketones, butadiene, ethylene oxide, glycerol, industrial solvents, styrenes, detergents and wetting agents, and also coal-tar types of aromatics.

So important has this by-product industry become, the primary aim of cracking now is to increase the yield of these materials, and not, as formerly, to obtain the highest possible yield of petrol and such products.

Mr. Carter concluded a most interesting address by stressing that all this development had occurred within the space of two decades, and was a triumph for engineering and chemistry.

Dr. J. K. Dixon, a Past President of the Institute, has been appointed Assistant Director of the Soil Bureau, Department of Scientific and Industrial Research, Wellington. An outline of his career was published in our issue for March, 1948, but it is also worthy of note that Dr. Dixon represents the D.S.I.R. on the Fertilizer Manufacturers' Management Committee, and on the Utilization of Organic Wastes Committee. He represented the Public Service on the committee that surveyed the scientific manpower resources of New Zealand, and is a Past President of the Wellington Branch of the Royal Society. Dr. Dixon continues to serve the Institute on the Salaries and Standard Methods of Analysis Committees.

We have been pleased to see a copy of volume I of the International Pharmacopoeia, published last year by the World Health Organisation. While of interest mainly to pharmacists, it will also interest chemists, firstly as a landmark in international co-operation, and secondly for the amount of chemical information it contains, particularly in the monographs on some of the newer drugs and the methods of testing them. The "Ph.I.," as it will be called for short, contains 199 monographs and 43 appendices in Vol. I, and may be obtained through the United Nations Association, Box 1011, Wellington.

The first meeting of the Canterbury Branch this year was held on Monday, 17th March, when Dr. R. Stern delivered her Chairwoman's address on "Oxidising Enzymes of Wheat."

On the 21st April, Mr. A. F. R. Adams, of Lincoln College, spoke on "Recent Trace Element Research in Australia."

Miss Campden-Cooke, of the Dominion Laboratory, Christchurch, is to go overseas shortly for a year or so.

Mr. H. B. Oakley, of Grasslands Division, D.S.I.R., has been seconded to the Internal Marketing Department and will take up his duties at their Vegetable Processing Plant at Pukekohe in the near future.

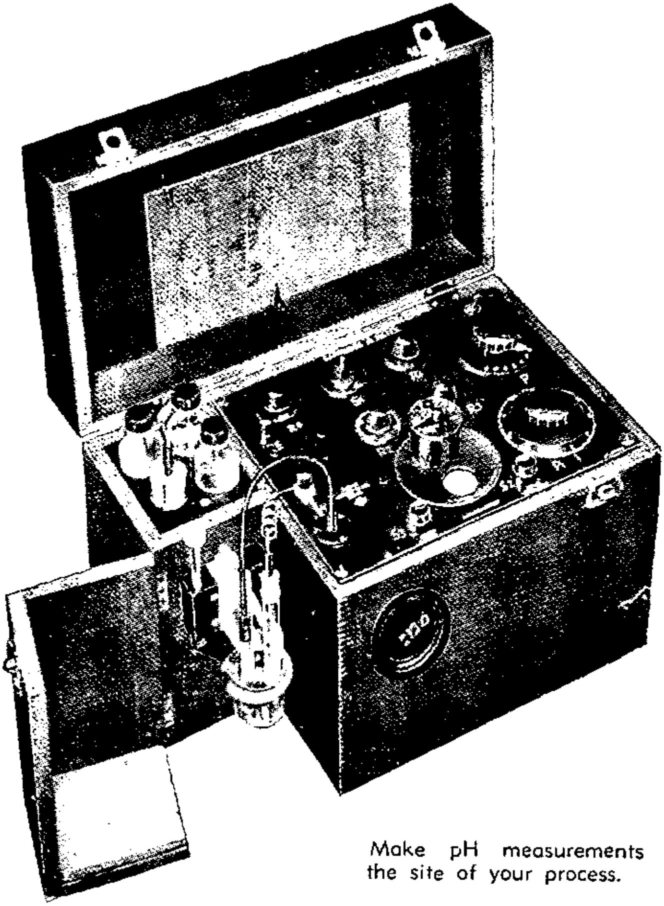
Mr. J. W. Ronaldson has joined the staff of the Ruakura Animal Research Station.

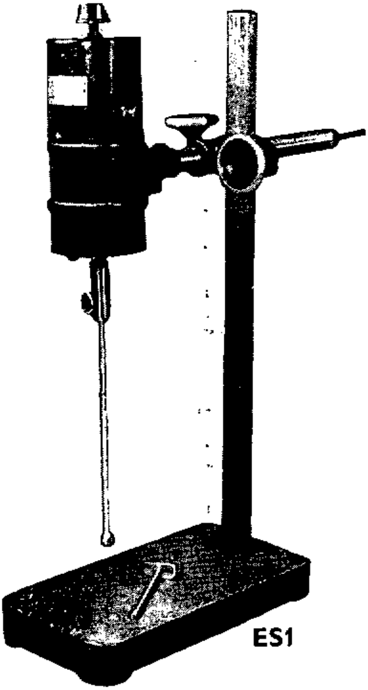
Mr. H. A. L. Morris is on temporary transfer to Auckland to undertake research into the curing of bacon.

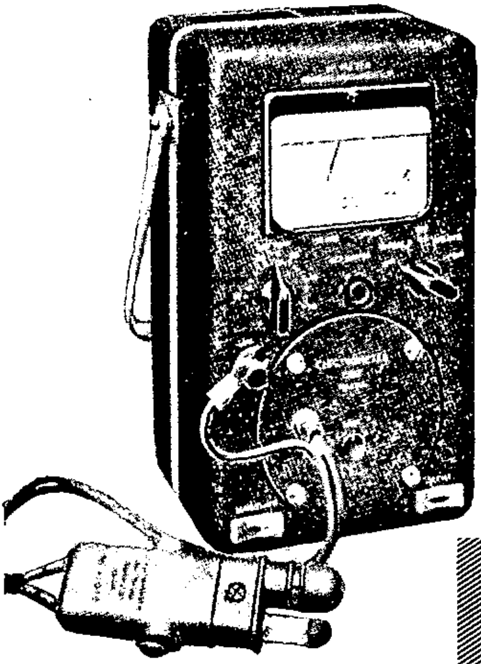
Dr. W. I. Taylor, at present working under Professor Todd at Cambridge on the constitution of alkaloids, including perloline, has been appointed Associate Professor of Chemistry, University of New Brunswick, Frederickton, New Brunswick, Canada.

Mr. L. D. Calvert has gone to Ottawa, Canada, having been awarded a National Research Council Post-Doctoral Fellowship. Mr. B. Cleverly has also been offered a similar fellowship. Both have completed their Ph.D. course at Auckland University College.

Mr. T. H. Kennedy, of the Thyroid Research Department, Medical School, Otago University, has returned after spending a year in England, during which time he was at the National Institute for Medical Research, although he also visited various University and Research Laboratories. (Sir Charles Harington, who first synthesised thyroxin, is the Director of the National Institute for Medical Research.)




ES1



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