40 minims (2½ c.cm.), and an adult dose should be from 50 to 80 minims (3 to 5 c.cm.), according to the size of the patient.

Finally, chenopodium is soluble in carbon tetrachloride, and a mixture of one part of the former in four of the latter should prove to be efficient for the expulsion of *Ascaris lumbricoides*.

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SOME OBSERVATIONS ON THE MECHANISM OF DRUG ACTION:

A STUDY IN PHARMACO-DYNAMICS.

BY

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IT has long been recognized that certain chemical compounds have very little effect upon the animal organism, whereas others produce a marked reaction when administered under similar conditions. The object of the present paper is to bring together some scattered observations which help to throw some light on such facts as these, and to explain the mechanism of pharmacological action. The subject will be dealt with under several headings, and the first one is naturally a consideration of the question of

Toxic Properties in Relation to Atomic Weights.

About the year 1815 Prout, who was a physician, published a paper in the *Annals of Philosophy* pointing out that in many cases the atomic weights of the elements were approximately whole numbers, and deducing from this that hydrogen was the primary matter from which all elements are formed by various condensations. The observations of Prout and the work of Newlands, Lothar Meyer, Mendelejeff, and others led to the well-known periodic classification of the elements.

This classification led to much valuable research and to many important discoveries, but apparently little has been written from the point of view of pharmacological relationships. A careful consideration of the periodic table reveals the fact that there are many relationships between the pharmacological reactivities of the elements (and their compounds) and their periodic grouping. A few examples will illustrate this point; if we compare the elements of the magnesium group we notice that the tendency is towards increase of toxicity with increasing atomic weight, the greatest toxicity being associated with mercury compounds. The oxygen group is also of interest, passing from a gaseous element to a typical solid non-metal, sulphur, thence to selenium and tellurium, with certain metallic characteristics. The hydrogen compounds of this series illustrate well the increase of toxicity with increase of molecular magnitude, starting with the innocuous substance water, and passing to the extremely toxic telluretted hydrogen.

A very valuable research was carried out by Michet[1] in 1881 on the relative toxicities of a number of metals. He experimented upon fishes with solutions of metallic chlorides, diluting the solutions so that the fishes could survive forty-eight hours in the diluted solutions. He applied the term "limit of toxicity" to the weight of metal present in the form of chloride which would be contained in 1 litre of such a solution. In his original paper he deplores the fact that no relationships between toxicity and atomic weight were observed. Unfortunately this is a case where an excellent research was largely thrown away from a scientific point of view by misinterpretation of the actual findings. Had he tabulated his results in weights proportional to atomic weights many relationships would have been revealed, but he was presumably ignorant of the nature of "molecular solutions." One example shows this fairly well.

	Michet's Values.	Michet's Values Recalculated and Multiplied to give whole Numbers.	Atomic Weight.
Calcium	2.4	600	40.0
Strontium	2.2	250	87.6
Barium	0.78	56	137.4

It is clear from this table that the toxicity of an element belonging to the same periodic family increases with increase in atomic weight, but, needless to say, such a law is subject to variations. It is highly improbable that such periodic relationships as have been referred to are accidental, and with increasing knowledge more light may be thrown on this interesting branch of pharmacology.

Influence of Solubility.

One of the factors long recognized as influencing pharmacological activity is the solubility of the drug concerned. There are so many well-known examples of this that it is quite unnecessary to refer to them in detail; it is sufficient to point out that in practical pharmaceutical chemistry various methods are used to increase the solubility of insoluble compounds; thus slightly soluble alkaloids are converted into more soluble alkaloidal salts, and in the realm of synthetic organic chemistry various groups are introduced into the molecule with the object of increasing solubility.

It has also been recognized that certain constituents of animal organisms exert a selective action in dissolving drugs introduced into the organism, and thus certain tissues are specially affected.[2]

Vapour Pressure.

Its vapour pressure is a factor of the greatest importance in its effect on the reactivity of the drug. For instance, chloroform, ether, and other volatile anaesthetics would be useless for the purpose if they did not possess a high vapour pressure. During the recent war the question of vapour pressure was of the utmost importance in connexion with gas warfare. It is terrible to think of the calamitous possibilities of easily prepared toxic substances possessing a high vapour pressure.

Relationships between Chemical and Pharmacological Reactivity.

The increased attention given to the synthesis of organic compounds during the middle and later years of last century has enabled chemists to determine the structure of chemical compounds and in collaboration with pharmacologists to demonstrate relationships between the chemical and physiological reactivity of drugs.

Some years ago[3] the rates of hydrolysis of a considerable number of anilides were investigated by the writer. These compounds, of which acetanilide (antifebrin) and phenacetin are common examples, owe their activity in part to the fact that they are hydrolysed slowly within the organism with liberation of the parent base according to the general equation—

$$R.NH.Ac + H.OH \rightarrow R.NH_2 + Ac.OH.$$

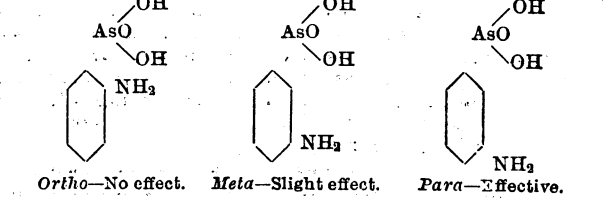
It was shown that there were definite relationships[4] between velocity of decomposition and degree of toxicity as previously determined by various pharmacologists.

Chemical Affinity.

In a further research[5] on isomeric substances having similar pharmacological action, it was shown that in certain cases chemical affinity and toxicity were quantitatively proportional. Such observations have more than a theoretical importance; for example, this difference in chemical affinity doubtless explains the differences observed by Breinl and Nierenstein when carrying out experiments upon trypanosomes with sodium salts of the isomeric amino-phenyl-arsenic acids. These observers found that the para compound, also known as atoxyl, is very reactive, the meta compound less so, and the ortho compound inactive.[6]

The relationship between the compounds is shown by the following formulae:

Arsenic Compounds.



Ortho—No effect. *Meta*—Slight effect. *Para*—Effective.

Another example of varying pharmacological activity is seen in the case of the isomeric hydroxy-benzoic acids, the ortho compound, better known as salicylic acid, being the only one possessing marked reactivity.

"*Affinity Constants.*"[7]

Ortho-hydroxy-benzoic acid	0.102
Meta-hydroxy-benzoic acid	0.00367
Para-hydroxy-benzoic acid	0.00286

Rate of Formation of Excretion Products.

In a paper referred to above[8] it was pointed out that the toxicity of a drug must partly depend upon the relative velocities of formation of "cell-drug" compounds and excretion products. To take a well-known example, the toxicity of hydrocyanic acid doubtless depends to some extent upon relative slowness of formation of excretion products as compared with the rate of formation of an active "cell-drug" compound.

A case which supports this theory may be referred to here—namely, that of the three isomeric aceto-toluidides whose rate of hydrolysis and pharmacological reactivity have both been investigated. The hydrolysis rates are as follows, "K" being a constant expressing velocity of hydrolysis:

	K.
Aceto-ortho-toluidide	0.709
Aceto-meta-toluidide	3.14
Aceto-para-toluidide	3.11

If the relative toxicity of these compounds depended only upon rate of hydrolysis it is obvious that the ortho compound would be the least toxic. This is not so actually, since the meta and para compounds are both non-toxic, the ortho derivative alone possessing toxic properties. This apparent anomaly may be readily explained by a consideration of certain observed facts. It has been found[9] that all three of these compounds may be oxidized with potassium permanganate to acetyl-amido-benzoic acids according to the general equation—

$$C_6H_4\begin{matrix}CH_3\\NH.COCH_3\end{matrix} + 3.0 \rightarrow H_2O + C_6H_4\begin{matrix}COOH\\NH.CO\,CH_3\end{matrix}.$$

Furthermore, it is known that acetyl-meta-amido-benzoic acid appears in the urine of dogs after administration of meta-aceto-toluidide.[10] That is, it is easier for the organism to excrete this compound as a relatively non-toxic product obtained by direct oxidation, rather than by oxidation subsequent to hydrolysis. A series of laboratory experiments have been made by the writer which demonstrate that the rate of oxidation of the ortho compound by potassium permanganate is much slower than that of the meta and para isomers under similar conditions.

It is thus seen that the only toxic isomer is the one which is least readily oxidized; in other words, a physiological reaction is produced at a greater rate than an excretion product of diminished toxicity can be formed.

Unsaturated Valencies.

The question whether or not the carbon atoms, and sometimes other atoms, in a chemical compound are saturated or unsaturated may have an important bearing on the pharmacological action of the compound. It has been recognized as a general rule that open chain derivatives containing unsaturated carbon atoms are more toxic than isomeric saturated bodies; thus allyl alcohol is fifty times more toxic than normal propyl alcohol.

Thiele[11] holds that in unsaturated compounds the combining energy of every atom which participates in the double linking is not completely absorbed, so that the atoms still possess valency (partial valenz), and it is in this partial valency that the source of reactivity is to be found.

Some light is thrown on the phenomenon of increased toxicity of unsaturated substances by comparing the properties of certain oxygen and sulphur compounds. It has been shown by Peters[12] that the replacement of oxygen by sulphur may increase "the residual affinity" of a compound. Thus one gram-molecule of silver cyanate absorbs one gram-molecule of ammonia, whereas one gram-molecule of silver thiocyanate absorbs two gram-molecules of ammonia under similar conditions. In a recent paper[13] on the influence of sulphur as a colour-producing element numerous examples are given in which the replacement of oxygen by sulphur produces coloured compounds from colourless ones, and it is shown that the heats of formation of the sulphur compounds are less than those of the correspounding oxy-compounds, supporting the suggestion that the substitution of sulphur for oxygen gives rise to less stable compounds, and that the chromogenetic properties of sulphur depend upon the formation of compounds possessing residual affinity. These observations are very significant when it is remembered that the replacement of oxygen by sulphur in chemical compounds frequently increases their toxicity; thus paraldehyde is a safe hypnotic with no action upon the heart, but tri-thio-aldehyde is a powerful heart poison. Carbon disulphide is also more toxic than carbon dioxide, and sulphuretted hydrogen, unlike its oxygen analogue water, is a very toxic substance.

Adsorption Phenomena.

The subject of adsorption has been dealt with by numerous workers, and has given rise to a large amount of literature; many theories have been advanced to explain the phenomenon, and it has been shown[14] that adsorption may consist not only of a surface action, but that this may be accompanied by diffusion inwards of material deposited on a surface. Some of the experiments referred to above extended over a period of eleven years, and were finally completed by Professor J. W. McBain.[15] These and other experiments have led to the belief that adsorption may play an important part in pharmacological action and pathological processes. Moore and Roaf,[16] who made laboratory experiments with anaesthetics upon brain tissue, etc., concluded "that anaesthetics form unstable compounds or aggregates with the proteids of the tissue cells, and that anaesthesia is due to a paralysis of the chemical activities of the protoplasm as a result of the formation of such aggregates."

In a recent paper[17] it is suggested that certain pathological states are initiated by the adsorption of toxins on the surface of specialized cells, and that if these surface layers be not removed permanent damage to the tissues may be brought about by the inward diffusion of these superficial layers. In this connexion it must be remembered that an extremely thin layer of adsorbed material may alter all the properties of the solid so covered,[18] and experience in the field of chemical reaction known as catalysis has demonstrated that adsorption layers are the seat of enormously enhanced chemical reactivity.

Idiosyncrasy.

Such an article as this would be incomplete without brief reference to the undoubted fact that some people exhibit a marked intolerance towards certain drugs, and conversely other individuals may be able to tolerate abnormally large doses of some special drug, and this must be borne in mind when attempts are made to compare the relative potencies of a series of chemicals. The writer was for a considerable period associated with a scientist who was able to inhale concentrations of noxious gases at least twice the magnitude that a normal man could bear, but after two years' work at such research his resistance in this respect broke down, and his sensitivity to gases became normal. It is not possible to explain such idiosyncrasies as this, but they are certainly of great clinical importance.

In conclusion, it is to be hoped that with increasing knowledge of the constitution of chemical compounds, combined with increased activity of experimental pharmacologists, in the near future the sciences of chemistry and pharmacology will be more intimately associated, to the mutual advantage of both scientists and clinicians.

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HEALTH conditions in the Ukraine remain disquieting, according to a report received from the Health Section of the League of Nations. Contrary to former experience at this time of the year, a very pronounced upward tendency of the typhus wave, with a heavy mortality rate, is reported. Cholera is also increasing. The needs of the moment are more than ever in excess of the resources of the Ukraine health administration, which is being forced to close one hospital after another.