# Department of Biochemistry and Microbiology

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Reviewing our work over the past 25 years, and trying to find a common denominator, I feel that all our activities in one way or another have been connected with metabolic inhibition. Two schemes will serve to illustrate this work.

When, in 1946, our Institute was founded, penicillin and streptomycin as well as sulphanilamide and DDT were still celebrating their first triumphs. Far less spectacularly the dithiocarbamates had made their start as agricultural fungicides. Encouraged by their outstanding performance, Klöpping began at our Institute in 1947, his investigations on the relation between structure and activity of these dithiocarbamate fungicides. Since then the synthesis of potential agricultural fungicides (Scheme I, 1) has remained a regular item in our research programme. Pluijgers, Niemann and Selling later investigated other groups of compounds and several thousands of such chemicals prepared by their „synthetics teams" were screened for fungitoxic activity at our Institute and elsewhere.

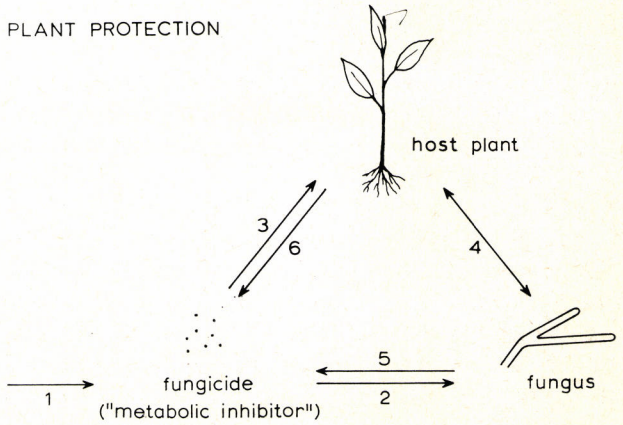
Apart from this synthetic line we soon tried to understand the mode of action of fungicides (Scheme I, 2), i.e. the way in which these inhibitors act on fungal metabolism. In such investigations remarkable difficulties can be encountered, for instance the fact that a compound can inhibit an enzyme system whose existence was not yet known. This happened in our investigations on the mode of action of the dialkyldithiocarbamates. We found that these compounds urge the fungus to accumulate pyruvate, but the true cause of this we could only recognize when later structure and function of the co-factor lipoic acid were revealed in the literature.

With our participation in the Research Group for Internal Therapy of Plant Diseases TNO, which was initiated by Professor Oort of Wageningen Agricultural University in 1951, our approach was greatly broadened through co-operation with phytopathologists. We were now immediately faced with the plant diseases and their control and, next to compound and fungus, the host plant was incorporated in our investigations as a third component (Scheme I, 3). One of the aims of this new research group was the development of systemic fungicides which should be taken up by the plant to protect it from within against penetrating fungi or those already there.

This problem was a real challenge to all participants of the group: The ideal systemic fungicide should be taken up by the plant, and be translocatable from leaf to root and from root to leaf, it should not be phytotoxic, and, last but not least, it should protect the plant against disease. One might expect that yet another primary condition should have to be fulfilled, i.e. that the compound should be toxic to the fungus in vitro. To our surprise, however, it appeared from our investigations as well as from those of other workers, that this is not an absolute requirement. Thus several growth regulators and also phenylthiourea, although not fungitoxic, are nevertheless able to protect certain plants against certain diseases. Investigations on the mode of action of phenylthiourea showed us that this inhibitor of polyphenoloxidase stimulates peroxidase activity in the plant. Its protective action may be due to these effects on the host.

Our investigations on the development of systemic fungicides were performed in close contact with the other members of the TNO Research Group and, also, with a team of a Dutch industry. Many compounds were prepared and screened; some showed very promising activity, but none ever reached the stage of practical application. Although this certainly is disappointing, we believe that our work may nevertheless have contributed to the development of interesting practical fungicides by research groups abroad.

After the successful practical achievements of these




*Scheme 1.*

systemic fungicides over the last few years, the aims of the research group, now headed by Professor Dekker, obviously undergo a change. We have learned to ask for every active compound whether it is active as such or whether a conversion product is the active agent. It remains important to know the biochemical mode of action of these active agents; at present it would seem that most systemic fungicides are inhibitors of biosynthesis rather than of energy-producing processes. Recently a new problem has turned up: the emergence of fungus strains resistant to the newer systemic compounds. Thus far this phenomenon had not been known in the application of fungicides and, at the moment, it it is difficult to predict to which practical implications this development of resistance will lead. No experience is yet available on resistance to practical fungicides of these mostly haploid and multinuclear organisms, which often easily form heterokaryons. Also from a genetical points of view, interesting problems thus arise.

I now return to our own attempts to develop fungicides. It will be clear that the fundamental question arose: How is resistance to disease effected in Nature? In other words: Why are of certain plant species, or varieties, some susceptible and others resistant to the same parasite?

We thought that a better insight into the biochemical aspects of natural resistance might give us new leads for the synthesis of effective fungicides (Scheme I, 4). We hoped to learn from Nature: „Natura docet". This accounts for our interest in the structure of naturally occurring fungicides. The structure of fungicides which are present, or easily formed, in elm trees was elucidated by Overeem in co-operation with Dr. Elgersma of the Laboratory for Phytopathology at Baarn; similarly in tulip bulbs (co-operation with Dr. Beijersbergen of the Laboratory for Flowerbulb Research at Lisse) and in apple leaf (co-operation with Dr. Raa). None of these compounds led to fungicides for practical application, nor did synthetically prepared derivatives.

Natural resistance generally does not depend on the occurrence of fungicides in plants. Knowledge on its true nature is, however, still very limited. For certain diseases we developed a hypothesis which was checked by Raa, Van Dijkman and Dieleman for apple varieties resistant to apple scab and for tomato varieties resistant to leaf mould.

These investigations on the biochemical differences between susceptible and resistant varieties led to the conviction that excretion products of the fungus damage the cells of the resistant host in such a way that, as a result, the fungus itself is killed. Thus fungus and plant mutually produce metabolic inhibitors for each other.

These investigations at the same time offer an explanation for the complicated genetic aspects of these diseases. Much co-operation in this work was given by the Institute for Horticultural Plant Breeding at Wageningen.

As mentioned before we first looked at the action of the compound on the fungus (Scheme I, 2) and on the plant (3). Conversely, one may ask what is the action of the fungus on the compound (Scheme I, 5) and of the plant on the compound (Scheme I, 6)? With these questions we are entering a different field of study, namely that of the protection of food and environment against contamination with pesticides.

Until recently attention was focussed on the development of fungicides possessing optimal properties with regard to plant protection and with minimum mammalian toxicity. A clearer insight into the possibility of partial conversions taking place in plant tissues and, also, into the hazards of contamination of the soil with pesticides, has added new requirements for the applicability of plant-protecting agents.

These considerations also added a new dimension to our investigations (Scheme II). In the first part of this paper, the pathogenic fungus obviously was the aggressor, which has to be combated by means of a fungicide. However, it may well be asked whether, after performing its task, the fungicide in its turn has not become the aggressor of our food and environment. Because a fungicide, like any pesticide, can in principle be a metabolic inhibitor of all kinds of organisms. Metabolism of the various organisms, apart from many differences, also shows great similarity. Therefore it will be desirable that, some time after application, no residues of the compound are left on the plant. If the compound has disappeared by breakdown, it is essential to know whether it either has been degraded completely, or whether more or less stable transformation products — „terminal residues" — are still present. Because these could, in principle, still act as inhibitors in plant, animal or man.

It is for this reason that at present one wants to be informed on the terminal residues of all pesticides which find wide application. Transformation of pesticides can be achieved either non-enzymatically, or by metabolic activity of plant, microbe or animal. Instead of terminal residue, the word „metabolite" is often used. To me, however, this term seems confusing. It should not be applied to compounds formed by non-metabolic processes.

For several years now transformation of pesticides has been a field of study of IUPACs' „Commission on Terminal Residues of Pesticides", which works in co-operation with FAO and WHO. In the Netherlands, relevant investigations are co-ordinated by the „Committee TNO for Research on Side-Effects of Pesticides".

With regard to the metabolic fate in plants of foreign compounds, like pesticides, only a few

years ago knowledge was lacking almost completely. When in 1961 Dekhuijzen established that dialkyldithiocarbamate fungicides in plants are converted enzymatically into three other compounds, it seemed an interesting observation of „merely fundamental" importance. The structure of the newly formed compounds has been elucidated by Kaslander, who also established that the conversion products formed by microbes and, in man, differed from those formed in plants.

Because of demands for the protection of food and environment, the interest in conversion products has greatly increased; four years ago the international IUPAC commission urgently requested us to undertake similar work on the conversion products of the related bisdithiocarbamate fungicides. This work, which is carried out by Vonk, has already resulted in the fact that we can expect traces of ethylene thiourea in treated plants. He found that this compound is highly stable in plants; it is a terminal residue of bisdithiocarbamates.

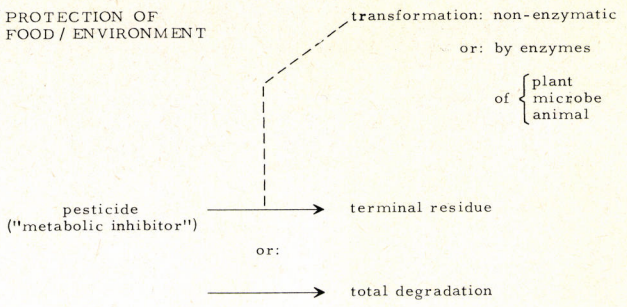
Meanwhile Dekhuijzen has started an investigation on the possible conversion of the growth regulator CCC, which finds application in cereals.

Not only our food, but also the environment must be protected, both against excessive use of pesticides, and against industrial waste. The life of plants, animals and micro-organisms is interdependent in a subtle way, more subtle than often is realized. In the cycles of carbon and nitrogen, in nature, micro-organisms in soil and water play the role of „chief scavengers" of organic material. On sites where those micro-organisms are unable to live, organic matter will accumulate.

Owing to their greatly varied patterns of metabolism, the various bacteria are able to metabolize even such compounds as mineral oil, methane, phenol, carbon monoxide, utilizing them as a source of food. Other compounds can be broken down when an appropriate source of food is present as well. However, their capacity to metabolize foreign compounds is not unlimited.

Due to the vast possibilities of synthetic chemistry, man tends to act as the chief polluter of nature; over the past years it has become clear that certain pesticides, or their terminal residues, and also certain industrial waste products can accumulate in the soil to an undesirable extent. The main threat appears to be from the chlorinated hydrocarbons and mercury compounds. The latter can accumulate to considerable concentrations in animals that are at the end of a natural food chain.

Mercury compounds deserve special attention, because a few years ago Swedish investigators showed that in the soil inorganic mercury compounds can be converted by certain organisms into the far more toxic and volatile methylmercury compounds. No knowledge is yet available as to which micro-organisms are capable to do so and under what conditions. We hope to contribute to a better understanding of this problem.




*Scheme 2.*

It will be clear that the accumulation of metabolic inhibitors is an extra threat, if such compounds act on the microbes which are responsible for the self-purification of the environment. The presence in grass or in drinking water of compounds which inhibit microbial growth may also threaten ruminants and other herbivorous animals which, for their digestion, have to rely entirely on the bacteria in rumen or gut.

One has to admit that there is a great lack of knowledge on the microbial potential to break down foreign compounds. Such investigations lag far behind the developments of synthetic chemistry. For the microbiologist this is an attractive field of study, and advantage can be taken of the many modern analytical detection methods.

As final items in this survey be mentioned the interesting work on other metabolic inhibitors, namely that of Dekker on inhibitors of cholinesterase and that of Dekhuijzen and Wakabayashi on herbicides and growth regulators.

Contacts with our Department for Organometallic and Coordination Chemistry are quite frequent. The synthesis of numerous organotin-, -lead and -germanium compounds with antifungal and antibacterial activity has provided us with rich material for study. The presumed site of action of these compounds could be given with reasonable certainty.

I have tried to give you a comprehensive picture of our work which mainly concerns problems of agriculture and public health. You will appreciate that our investigations are based on an intense and stimulating co-operation between chemists and biologists, each of whom is a specialist in his particular field of study.

# Department of Organometallic and Coordination Chemistry

Dr. J. G. NOLTES

Contrary to the situation for most of the main areas of research within the Institute for Organic Chemistry TNO, the initiative to take up research in the area of organometallic chemistry has not been generated from within the Institute. The first contact of the Institute with this branch of chemistry, which at that time was still rather uncommon, occurred in 1949. The International Tin Research Council, London, then commissioned the Institute to carry out an explorative study of organotin chemistry with the principal aim of uncovering new applications for organotin compounds and, thereby, develop new markets for tin. When, in 1950, the organotin programme was set up, there was no indication that in doing so the Institute had entered an area of research which, in the following two decades, was to manifest itself as one of the most rapidly developing areas of chemistry.

The foundations for the rapid growth of organometallic chemistry in recent years had been laid a considerable time before. In fact, the early history of, organometallic chemistry and that of organic chemistry date back to the same period and they show some strong interrelations. Noteworthy historical developments, which I can mention only briefly, include the pioneering studies of the German chemist Bunsen, who in the early 1840's worked with organic derivatives of arsenic, and those of the English chemist Frankland, who some ten years later isolated organometallic derivatives of zinc. Frankland's studies, which were initially aimed at obtaining the organic radicals methyl and ethyl, were to play a major role in the development of the valence theory of chemical elements. Another milestone, the importance of which is not easily overrated, forms the discovery in 1900 by the French chemist Grignard of a simple synthesis of organomagnesium halides; later these were to find wide application as synthetic intermediates in both organic and organometallic chemistry. Fundamental to Grignard's discovery was the use of diethyl ether, a solvent with strongly coordinating properties, for the reaction of organic halides with metallic magnesium. It is interesting to note that a contemporary of Grignard, Alfred Werner, in the same period laid the foundations for modern coordination chemistry. In 1902, Werner formulated the concept of principal and auxiliary valence, a concept wich plays a predominant part in the Grignard reaction. Both Grignard and Werner were to be awarded a Nobel prize for chemistry, in recognition of their fundamental contributions to the development of organometallic and coordination chemistry.

In principle, Grignard's discovery opened up opportunities to prepare compounds of practically all elements containing one or more element-carbon bonds, simply by the reaction of compounds that contain one or more element-halogen bonds with Grignard reagents. In fact, it was predominantly this aspect — expansion of the number of known organometallic compounds — which for the next fifty years was going to occupy the relatively few chemists involved in organometallic research.

In 1950, when the Institute for Organic Chemistry TNO took up the organotin project, organometallic research lacked a systematic approach, in particular as regards the search for applications. This is the more surprising as an industrial development of extreme importance had meanwhile taken place. I am alluding to the discovery of the American chemist Midgley, in 1922, that incorporation of tetraethyllead in gasolines suppresses the reactions that, in the internal combustion engine, produce the undesirable phenomenon of knock. The significance of this discovery was such that, within a few years, tetraethyllead was being produced on an industrial scale. It is perhaps best illustrated by the recent production figure for alkyllead antiknock agents of about four hundred thousand tons annually representing about fifteen percent of the annual world production of lead. Apart from the fact that this development has placed the tetraalkylleads among the most important industrial synthetic organic chemicals, we see that this organometallic application opened up a market for lead that is entirely new for this metal. However, this turned out to be an incidental development which, moreover, failed to produce an intensification of organometallic research.

When looking back at the time when, in 1950, Dr. J. G. A. Luijten synthetized the first organotin compounds at the Institute for Organic Chemistry TNO, it appears that this moment more or less coincides with a new development phase for organometallic chemistry which, once on its way, has proceeded almost explosively to the present day.

Apparently the time had grown ripe for the exploration of interdisciplinary areas of research, of which organometallic chemistry as a borderline area between organic and inorganic chemistry would seem to be a classic example. It soon became apparent that the Institute for Organic Chemistry TNO, by embarking upon an organometallic research project, had made a timely and fortunate move. The results obtained through the organotin research programme, some of which I will mention briefly, were given appropriate publicity through lectures and scientific publications. When, at the close of the nineteenfifties, several international research organizations decided to follow the example set by the International Tin Research Council, the association between our Institute and organometallic research had meanwhile become quite close and accordingly, the Institute for Organic Chemistry TNO was selected as a partner for a number of research cooperations.

In connection with a research project aimed at incorporating IVth group organometallic radicals into high-molecular weight polymers, we had gained our first experience with the chemistry of organometallic compounds derived from silicon, germanium and lead. In 1959, the Germanium Research Committee, Brussels, decided to sponsor at OCI an explorative research programme of organogermanium chemistry. In 1960, the International Lead Zinc Research Organization, Inc., New York, took up sponsorship of an explorative programme in organolead chemistry and in 1962 this was extended with a programme in organozinc chemistry. Meanwhile, the Institute since 1957 had also become active in transition metal organometallic research through an industry-sponsored project dealing with organovanadium chemistry. With the exception of the organo-germanium project, the research programmes sponsored by the international research organizations have been continued till the present day. Since 1968 we have been involved also in explorative reserach on organocopper chemistry, a project sponsored by the International Copper Research Association, New York. The international research organizations mentioned did not themselves have facilities available for carrying out organometallic research, nor did they have the required background knowledge for carrying out such research. The job of developing novel organometallic chemistry and new application possibilities for tin, germanium, lead, zinc and copper was entrusted to the Institute for Organic Chemistry TNO. In addition to these metals, the Department of Organometallic and Coordination Chemistry is at the present moment involved in explorative organometallic programmes dealing with silver, indium, antimony and bismuth as well as in transition metal organometallic research. This work is partly sponsored by industry.

The number of metals mentioned clearly illustrates the growth of organometallic research at our Institute since 1950. In addition to the long-term research projects, the Department works on short-term projects of a limited scope, each aimed at the solution of clearly defined problems, such as an improved synthesis for a specific organometallic compound. In this type of projects, the problems are often solved on the basis of knowledge already available; it is not necessary — as has often been the case in our long-term research projects — to develop the basic knowledge more or less from scratch.

In all our organometallic research, investigation of properties of newly synthetized compounds and the question „which possible use may these compounds serve?" have been, and are, brought into focus. In fact, our research has always been dualistic in nature. One part relates to the development of novel chemistry, in particular the synthesis and characterization of hitherto unknown types of organometallic compounds. In line with our firm belief that new chemistry offers the best basis for new applications, these studies have often been quite fundamental. The other, and equally important, part of our research is aimed at developing new applications for organometallic compounds or at improving existing applications. Considerable attention is also being paid to developing more economical manufacturing methods for compounds of proven applicational value. The Institute has made it an item of policy to give the widest possible dissemination to its research results, whenever this is possible. Over the years numerous papers describing the more fundamental aspects of our research have appeared in print, and the work has moreover been discussed in a great many lectures. In numerous cases, research results have been laid down in patent applications. Time does not allow to discuss the very extensive and active contacts concerning our organometallic research that have existed over the years between the Institute for Organic Chemistry TNO and industrial and government laboratories all over the world. These numerous, mutually beneficial contacts lend an extra, very valuable dimension to the organometallic programmes.

To cope successfully with the many and often much diversified aspects of the various organometallic programmes, close cooperation with the other Departments of the Institute is a primary requirement. An adequate approach to those projects calls for application of various spectroscopic, analytical and other techniques. This indispensable support is provided by the Physical-Organic and Analytical Chemistry Department. With a view to the rapid development of physico-chemical techniques, and the increasing complexity of the interpretation of the data, the importance of this cooperation is still growing.

Cooperation with the Biochemical and Microbiological Department dates back to the very beginning of our organometallic research. It must be considered a very fortunate circumstance that, at the start of our organotin programme the Institute had a research group capable of performing a screening for biocidal properties of the compounds resulting from work under this programme. This, already in 1950, led to the discovery that triorganotin compounds display interesting fungicidal properties. This fundamental observation was followed by a very extensive screening programme and, without going into details, we see that this research has formed the basis for the present day use of triorganotin compounds for a variety of applications. As an example I mention the application in numerous countries of triphenyltin compounds as an agricultural fungicide for fighting economically important fungal diseases of plants, such as phytophthora with potatoes. I might add that the OCI played an important role in developing the methods of synthesis for these compounds that are now applied by industry.

At a later stage, structure-specific biocidal properties have been observed for other types of organometallic compounds developed at OCI. It is outside the scope of my present talk to discuss in detail the results of various extensive screening programmes set up in cooperation with industrial and government laboratories with the purpose of developing practical applications based on observed biocidal properties, such as those of antifouling paints for ship bottoms, fungicidal paints, as preservatives of textiles or wood against attack by microorganisms, and the like.

I should, however, like to provide one example which may serve to illustrate that progress in one area may make itself felt in areas which, at first sight, seem totally unrelated. Investigations at OCI aimed at elucidating the relationship between chemical structure and fungicidal activity of organotin compounds — in particular the influence of the chain-length of alkyl groups in alkyltin compounds — revealed that alkyltin compounds with longer alkyl chains ($> C_6$) display negligible fungicidal activity. This observation led to further research (in cooperation with the Plastics and Rubber Research Institute TNO) related to the possibiliy of applying diorganotins with long alkyl groups as non-toxic stabilizers for polyvinylchloride. In fact, dioctyltin compounds turned out to be fully acceptable from a toxicological point of view (low toxicity combined with a low extractability from the finished products), whereas the stabilizing activity turned out to be fully comparable with the commonly used dibutyltin compounds. This research has led to the present day, large-scale use of dioctyltin compounds as non-toxic stabilizers for PVC used as packaging material.

A second area of research which is fully in line with the application-oriented philosophy of the Institute is that of finding applications for organometallic compounds in the general field of catalysis. Since Ziegler in the early mineteenfifties discovered multi-component organometallic catalysts for the polymerization of olefins, interest in the possibility of developing novel organometal-based catalyst systems has strongly increased. At the Institute for Organic Chemistry TNO, a large variety of organometallic compounds has become available through the various research programmes. More recently, a systematic study has been devoted to the possibility to realize, for some of these compounds, applications in the area of catalysis. Time does not permit to discuss in detail the surprisingly varied catalytic effects which have been uncovered in the course of these investigations; for example the formation of poly-urethanes catalyzed by monoaryllead compounds, or the different types of organozinc-catalyzed processes which include the stereospecific polymerization of acetaldehyde, the alkylation of aromatic compounds and the stereospecific cyclotrimerization of butadiene. I mention briefly that at the OCI novel types of multicomponent organometallic catalyst systems have recently been developed; they allow the rapid, virtually quantitative polymerization under mild conditions of epoxides such as propylene oxide and epichorohydrine. The catalysts afford polyepoxides with a high degree of crystallinity which, moreover, in dependence on the type of catalyst used can be predetermined. In this way thermoplastic propylene oxide homopolymer with rubbery properties has been obtained. Whereas the Ziegler-Natta catalysts contain a transition metal compound as a characteristic ingredient, our new catalysts are based on the combination of two main-group organometallic compounds and are thus of a novel type.

In recent years, investigations concerned with organometallic coordination complexes and organic metal complexes have been increasingly incorporated in the programme of the Department. In this connection it is relevant to note that, in numerous biological systems, metals in the form of metal complexes which keep the metal in a fixed stereochemical position play an essential role. More and more the study of heavy metals in biological systems has become inter- and multidisciplinary in nature. I am thinking for example of the problem of nitrogen fixation which is tackled in a variety of ways. These studies range from an investigation of the role of metal atoms (iron and molybdenum) in a cell-free nitrogenase enzyme system to the activation of the „inert" nitrogen molecule by transition metal compounds; investigations which have already allowed the catalytic conversion of nitrogen into hydrazine, catalytic conversion into ammonia being, of course, the ultimate goal. This area of organometallic and

coordination chemistry, which is equally connected with organic, inorganic and biochemistry, would seem to fit in naturally with the research programme of the Institute.

Another area where organometal complexes play an increasingly important role is that of catalysis. Present day industrial chemical processes are for the greater part based on a large variety of catalytic effects of metal compounds, in particular transition metals. Until relatively recently the word catalysis, in this connection, had remained synonymous with heterogeneous catalysis. However, in recent years industrial processes have come to be realized which make use of transition metal derivatives as homogeneous catalysts. The best known examples of such homogeneous processes are perhaps the hydroformylation of olefins, the so-called „Oxo-process" and the oxidation of ethylene to acetaldehyde, the so-called „Wacker process". When it was realized that, in these reactions, organometallic compounds occur as labile intermediates, interest for the chemistry of transition metal organometallic complexes, in particular their application as homogeneous catalysts, received another strong stimulus. Homogeneous catalysts possess a well-defined and fixed stoichiometry and structure, and thereby have the advantage of perfect reproducibility. Their catalytic activity is determined by a variety of factors, such as the nature of the metal, its valency and the nature and stereochemical position of the ligands bound to the metal. If the influence of these various factors is better understood — and considerable progress has already been made in this respect — it may turn out to be possible to tailor-make homogeneous catalysts which are more efficient and, in particular, more selective than the heterogeneous catalysts now in use.

This area of organometallic and coordination chemistry which branches out to industrial chemical processes on the one hand, and to fundamental biochemical processes on the other, has generally come to be considered as potentially the most important of the whole field. It is relevant to note that, in Great Britain, the Science Research Council when defining areas of chemistry deserving of special financial support recently singled out the area of organometallic and coordination chemistry for an additional grant of £ 300.000 annually.

The forecast that within twenty years perhaps half the catalysts employed by the heavy organic chemical industry will be organometallic in nature has evidently contributed to this decision being reached. Should British research lag behind in the development of these catalyst systems, Britain will predictably be faced with a bill for exported royalty payments in the region of £ 15 million a year by 1980. However, if even one or two of the important catalyst systems of the 1980's are British innovations, the country may earn about the same amount in imported royalty payments. These are indeed no minor considerations!

Within the Department of Organometallic and Coordination Chemistry, transition metal organometallic research was until recently performed on a more or less incidental basis. Some time ago, a decision was taken to set up, within the Department, a research-group which will be specifically involved in transition metal organometallic chemistry with main emphasis on aspects of homogeneous catalysis of organic chemical reactions.

Modern organometallic and coordination chemistry is a fast moving branch of science, and it is of ever increasing complexity. The Institue for Organic Chemistry TNO, in view of its past and present performance, may be expected to continue making contributions to this field. Provided appropriate means are made available, there is good reason to assume that, with the competence and enthusiasm of my colleagues as a sound basis, this challenge can be met successfully.