proved active, not only against erythrocytic but also against the exoerythrocytic forms of the experimental avian parasites, and one such derivative, proguanil ('Paludrine': N^1 -*p*-chlorophenyl- N^6 -isopropylidiguanide), has passed into extensive clinical use on this basis.

As a result of these war-time endeavours, the objectives initially postulated have been largely attained. The causative organisms of malaria are so numerous in variety and drug susceptibility, however, that some forms of the disease inevitably remain resistant to therapy if only in degree, and the existence of these, together with the problem of relapse in certain cases, provide the challenge for the future.

In the concluding paper of the session, Mrs. R. V. Pitt-Rivers described recent work on the thyroid gland. She pointed out that the biosynthesis of thyroxine depends on the ability of the thyroid gland to collect iodide from the plasma and to fix it in organic combination. In the normal animal, the iodine-concentrating mechanism is largely controlled by the thyrotrophic hormone of the anterior pituitary, and fails in hypophysectomized animals. Thiocyanate inhibits the iodine-concentrating mechanism and, in fact, causes the discharge of iodide already collected by the gland. The second function of the thyroid, the synthesis of thyroxine, is generally assumed to occur in three stages: (a) oxidation of iodide to iodine, (b) iodination of tyrosine, and (c) coupling of two molecules of diiodotyrosine. The first stage requires enzymic activity, but this is not necessarily so for the coupling reaction, as coupling can occur *in vitro* in the absence of any enzyme system. Dr. Pitt-Rivers has found that if the amino group is protected by acylation and the carboxyl group by peptide combination, then the yield of thyroxine formed by incubating diiodotyrosine aerobically can be raised to 35 per cent. The coupling is an oxidative one, but its mechanism is not known, nor is the fate of the three-carbon chain which is lost from one molecule of diiodotyrosine.

Dr. Pitt-Rivers outlined experiments with anti-thyroid drugs of the thiourea group and also with aniline derivatives which include *p*-aminobenzoic acid and some of the sulphonamides; these have led her to conclude that the formation of thyroxine from diiodotyrosine is an oxidative reaction brought about *in vitro* by small amounts of iodine liberated from the diiodotyrosine. In *in vivo* experiments, too, the formation of thyroxine is invariably accompanied by loss of iodine from diiodotyrosine. The remarkable inhibition of thyroid function by iodide is possibly due to an inhibition by excess of iodide of the enzyme system which is responsible for its own oxidation.

Finally, Dr. Pitt-Rivers showed how the use of new techniques, in particular the use of radioactive iodine and partition chromatography, has enabled several groups of workers to localize reactions in which iodine plays a part, and to detect iodo compounds which are present in the gland only in traces. Apart from diiodotyrosine and thyroxine, the only iodine compound present in the gland which has been unequivocally characterized is monoiodotyrosine. All three compounds are present in the thyroid in very small amount as free amino-acids, and three new iodine-containing compounds of unknown constitution have been detected in the gland. Evidence has been provided that the circulating hormone in the plasma is free thyroxine.

AUTOMATIC CONTROL

A CONFERENCE organized by the Department of Scientific and Industrial Research, on the subject of developments in the field of automatic control, was held at the College of Aeronautics, Cranfield, during July 16-21, under the presidency of Sir Ben Lockspeiser. It was attended by some three hundred engineers, mathematicians and teachers of engineering, including members from most of the leading industrial countries.

The purpose of the present article is to give an impression of the state of developments in the field of automatic control as revealed by the papers and the discussion at the conference. The broad principles of automatic control involving feed-back are now very well known, and many useful methods for the analysis of the behaviour of control systems are quite familiar. The conference was concerned with those aspects of the subject that go beyond these well-established principles and methods and in which further progress is required. The chief topics may, perhaps, be broadly classified as follows: first, educational problems arising from the growing importance of feed-back systems, and the rapid increase in the demand for personnel having specialized knowledge and skills in this field at all technical levels; second, the development and co-ordination of improved methods of mathematical analysis for such systems; third, the extension of the methods to a widening range of technical and other problems; and finally, the attempt to deal more adequately with such problems as systems with non-linearities and with intermittent data. In attempting to give a summary of the present state of progress as revealed by the conference, it will be convenient to consider these four topics in turn.

Educational problems. New requirements in respect of instruction in the principles of automatic control are arising over the whole educational spectrum, from the shortage of instrument mechanics in the chemical industries to the need for more men of the highest engineering and mathematical competence to carry on development work in such fields as the control of aircraft or the development of combined analogue-digital calculators.

The opening paper of the conference by Prof. Gordon Brown, of the Massachusetts Institute of Technology, made a striking plea for the recognition of the "feed-back engineer" as a new professional category corresponding with a new type and perhaps a new standard of professional competence. The specification for a feed-back engineer is for a man capable of synthesizing many technical specialisms and capable of eliciting co-operation at all technical levels. Prof. Brown described the postgraduate school in control engineering at the Massachusetts Institute of Technology, which has an annual output of approximately fifty postgraduate students. This figure was referred to by a member from a leading American instrument firm as "merely a drop in the ocean of America's requirements". Prof. Brown described how students are trained at the Massachusetts Institute as working engineers participating in large-scale research projects, accepted by the Institute on contract. Such forms of advanced technical training are unknown in Great Britain, where it is noteworthy that the research establishments of government departments and of the research associations have no specific educational functions and not even in organized liaison with higher education.

Progress in methods of mathematical analysis. The analysis of the behaviour of linear systems with feed-back corresponds with the discussion of the implications of a set of simultaneous linear differential equations. Since complex as well as real roots are in question this naturally leads to representation on the complex plane. The types of analysis that have been developed for application to feed-back amplifiers, networks and filters are generally applicable to linear automatic control systems. Developments now being made in this type of analysis, as indicated by one group of papers presented at the conference, may be described as the exploration of the geometry of poles, zeros and 'transfer loci' on the complex plane, in the attempt to obtain various kinds of information about the behaviour of the system, such as its modes, their kind and degree of damping, and the conformity with various criteria of stability and minimum error. A particularly interesting development arises from the fact that the functions involved are usually regular functions, and such functions of a complex variable have a correspondence with the flow-lines and equipotentials for current flow in a conducting sheet. This fact has been ingeniously exploited by A. R. Boothroyd and J. H. Westcott, who described and demonstrated the use of the electrolytic tank as an analogue interpreting a logarithmic transformation of a complex variable, by the use of which the design of both control systems and filters may be facilitated.

An important problem requiring distinct treatment arises when control systems are subject to random disturbances. Two papers, respectively by M. J. Pélégryn and S. Jones, dealt with the application to control systems of the method based on statistical ideas and correlation that was originally developed by Wiener.

The view was expressed by several contributors that, important as these improvements in analysis may be, they must, by their nature, be deficient in meeting the basic problem of the selection and design of control elements, because they do not bring under consideration the physical limitations of the elements that are essentially related to power handling and the interchange and flow of power. One paper only grappled with this problem of relating the design of machine elements to the specified power amplification and the limitations of rating. This was the paper by J. M. Layton, in which some useful first steps are taken in this direction, by introducing the relationship that arises between the time constants and the power amplification in any element (such as an electric generator) in which there is energy storage proportional to the power output.

Extension of control system theory to a wider range of problems. One of the most important and rapidly expanding fields for the application of automatic regulation and control is the chemical and process industries. A complete day of the conference was devoted to this field. This was deliberately placed in the middle of the conference programme, because the organizers thought that one of the needs of the moment is to throw 'process engineers' and 'servo engineers' into intimate contact. This plan resulted in a vigorous discussion, somewhat hampered by difficulties of language, and by the unfortunate fact that each party appears to the other to plot all its diagrams back to front and for the inverse variable. It may be unfortunate that those now attempting to establish standardization of terms have abandoned the effort to reconcile those of process engineering with those of 'servos', and propose to perpetuate the

differences. Perhaps a few years of delay and more such joint meetings would convince both parties that a common nomenclature would be both possible and useful.

The papers presented under the general heading of process control dealt mainly with the calculation and measurement of the transfer functions of pneumatic controllers and of plant elements such as pipe-lines and heat exchangers, in a form that permits of the use of this information in the familiar 'frequency-response' type of analysis.

Automatic-control principles are constantly finding application in new and somewhat surprising contexts. For example, A. Garde, of Stockholm, described an experimental investigation of the response of frequency to power load for a complete power system that involved the artificial imposition of a sinusoidal variation of power of 15 MW. as the test signal.

The theory of control systems is mainly a discussion of systems in which a number of variables, often a large number, are interdependent or inter-related, that is, some of the sequences of dependence are closed. This situation arises in many scientific fields, and when it is required to discuss the behaviour of such systems the methods of the theory of control systems may be useful. A good example is in economics, where much recent work concerns the implications of given inter-relationships between 'macro-economic' variables such as total income and total investment. This topic was the subject of an informal evening lecture given by J. R. N. Stone, of Cambridge, with a short addendum from an engineer's point of view by Prof. A. Tustin. It was urged that the interpretation of the implications of the rather complex 'models' necessary to give adequate representation of an economic system might be assisted by the use of physical analogues, as is often done in the case of complex engineering problems.

Special problems: intermittent data and non-linear systems. Groups of papers were devoted to the two chief aspects of control system analysis which the usual linear theory omits.

The first type of problem is that in which the system may be linear in the sense that it satisfies the principle of superposition, but where the operation is essentially discontinuous. One familiar example arises when 'clamped' or 'chopper bar' regulators are used, that measure a continuous variable at fixed equi-spaced instants, but between these instants merely hold or 'clamp' the value from the preceding measuring instant. A very analogous problem arises when incoming data is in digital form, giving effectively the value of a set of equi-spaced ordinates of the input curve. The handling of such problems will be greatly facilitated by papers included in this conference. The contributions by Prof. C. Holt-Smith, D. Lawden and A. E. Bailey, and the papers by Dr. R. C. Oldenbourg and Dr. H. Sartorius from Germany, make a noteworthy advance on previous work.

One day of the conference was given to the different problems that arise when systems are non-linear. Among those present for this discussion were such well-known authorities as Prof. B. van der Pol, Dr. N. Minorsky and Dr. Mary L. Cartwright, and the discussion was on a high level even if it mainly showed once more the unfruitfulness, so far, of attempts to deal with most non-linear systems except to seek specific numerical solutions to specific problems. A possible point for future progress lay in the paper by C. Cherry, in which he returned to

fundamentals, and showed by adapting the equations of Lagrange that in certain systems the part played by energy in linear systems is played by areas under a curve in the case of non-linear systems.

Manual control as distinct from automatic control was not forgotten. The paper on this subject by J. D. North included a thorough analysis of a 'model' that may provide a useful approximation for the response of hand to eye in some simple situations such as target tracking or car driving.

The discussions throughout the conference were vigorous and sustained. It appeared to be the opinion of all who attended that the conference has helped to lay foundations on which much further progress may now be based.

The papers presented, together with selected material from the discussions during the conference, will be published in due course as a single volume by Butterworths Scientific Publications, Ltd.

A. TUSTIN

STRUCTURE OF RIBONUCLEIC ACID

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IN the past few years the basic constitution of several ribonucleic acids has been established¹⁻⁴, but so far there has been little evidence as to the way in which the constituent nucleotides are arranged in the molecules. Hydrolysis of ribonucleic acids by alkali and by cold dilute acids gives rise to isomeric nucleotides which are probably 2' and 3' nucleoside phosphates⁵⁻⁷, and Cohn and Volkin⁸ have recently also identified 5' nucleoside phosphates in ribonucleic acids digested successively with both ribonuclease and alkaline phosphatase. In the work which we propose to describe, we have attempted to isolate the larger fragments produced by ribonuclease action, and we have succeeded in establishing the structure of certain of the dinucleotides which were formed.

Anhydrides of the Pyrimidine Nucleotides

In our investigation of the products of digestion of ribonucleic acids, our attention was drawn at once to the presence of two substances which we have called *C* and *U*⁹. These substances are digested slowly by ribonuclease to give free cytidylic and uridylic acids respectively, and each contains one atom of phosphorus per pyrimidine residue. They differ from the nucleotides in that they have higher R_F values in 70 per cent v/v isopropanol-water-ammonia (solvent *a*), and lower R_F values in 80 per cent saturated ammonium sulphate in water, 2 per cent isopropanol, 18 per cent *M* sodium acetate (v/v/v) (solvent *b*). These properties led us to believe that they contained less free hydrophylic groups than exist in the corresponding nucleotides, possibly because they were dinucleotides or dinucleoside pyrophosphates. When we were doing this work, we were fortunate in having a discussion with Prof. A. R. Todd and Dr. D. M. Brown, and they were kind enough to disclose their theory of the formation of the isomeric nucleotides of Carter and Cohn. This theory⁷ necessitates the existence as

intermediates during the chemical hydrolysis of ribonucleic acids of cyclic anhydrides of the nucleotides, which have the phosphoric acid residue esterifying the ribose at positions 2' and 3'. Such substances would have the properties of our *C* and *U*, and, in addition, would have the same electrophoretic mobilities as the corresponding nucleotides at pH 3.5, as do *C* and *U*, while, as we will show, the electrophoretic mobility of a dinucleotide should be about 1.54 times that of a mononucleotide having the same constituents. Synthetic samples of the anhydrides of cytidylic and uridylic acids prepared by Mr. D. Magrath were chromatographed by us in several solvent systems and could not be distinguished from *C* and *U* in any of these, while they too were digested slowly by ribonuclease to give the free nucleotides. It seems very likely that *C* and *U* are the 2', 3' anhydrides of cytidylic and uridylic acids respectively. The analogous adenine derivative was not digested by ribonuclease, and it seems probable that the guanine derivative is also resistant to digestion.

Free Nucleotides and Polynucleotides

For preparing these substances we have digested purified yeast ribonucleic acids with ribonuclease in dialysis sacs at 20° and also at 4° with stirring, so that any fragments liberated should have a chance to escape further digestion. After concentration *in vacuo*, the dialysate has been chromatographed in solvent *a* on Whatman No. 3 paper in bands. The developed chromatograph shows a residue at the top (band 0) and six main bands numbered 1-6 in order of their R_F values. Band 6 contains *C* and *U* only. Bands 1, 2 and 3 contain compounds of all four bases, while bands 4 and 5 have no guanine derivatives. Band 4 contains only adenylic acids *a* and *b*, cytidylic and uridylic acids. Free guanylic acids *a* and *b* are found in band 2. Bands 3 and 5 contain substances having properties similar to *C* and *U*; that is, they are digested by ribonuclease to give substances running faster in solvent *b* and slower in solvent *a*, but without changing their gross analytical composition. The analyses, however, show that each band contains several substances, as the purine and pyrimidine bases are not present in simple proportions.

Electrophoretic Separation

After trying without success a number of solvent systems for separating the substances in each band, we decided to try electrophoresis on filter paper strips, immersing the wet filter paper in carbon tetrachloride to cool it and to prevent evaporation. Strips of Whatman No. 3 paper 56 cm. long and 8 cm. wide were used, and the material was applied about 12 cm. from one end. A voltage gradient of 20-25 V./cm. was used and the average run was two hours (Fig. 1).

Before attempting the separation, we calculated the probable relative electrophoretic mobilities of all mono-, di-, and some tri-nucleotides at several pH values, using the dissociation constants of Levene and Simms¹⁰, assuming that the mobilities were proportional to the net charge on the molecule, and inversely proportional to the cube root of the molecular volumes, a relationship which should hold to a close approximation in the case of such asymmetrical molecules, and which has been found to hold with some minor deviations in practice. The