BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 16 1959

PROTEIN METABOLISM OF THE BRAIN*

BY

DEREK RICHTER, M.A., Ph.D., M.R.C.S., L.R.C.P.

Director, Medical Research Council Neuropsychiatric Research Unit, Whitchurch Hospital, Cardiff

Protein Metabolism During Growth

Growth involves the synthesis of the proteins and lipoproteins, which together make up some 90% of the dry weight of the brain. The growth of the brain proceeds ahead of most of the other organs of the body, since it is needed relatively early in life as a controlling centre for the neuro-endocrine functions of the body, and in the embryo of five days the brain accounts for as much as 30% of the total body weight. The activity of the enzyme systems concerned in protein synthesis is indicated by measurements of the rate of incorporation of amino-acids labelled with radioactive isotopes. Protein formation in the 13-day embryo, as indicated by the uptake of ^{14}C -glycine, is about twice as fast in brain as in liver tissue (Greenberg *et al.*, 1948). The relatively high rate of protein synthesis in the brain gradually recedes until the rate in the brain is similar to that in other tissues, and in the adult animal the rate of incorporation of amino-acids in isolated brain tissue is intermediate between that of heart muscle and liver.

The synthesis of new protein continues during the first few years of life at a rate corresponding to the rapid increase in size and weight of the brain. The water content of the foetal brain is higher than that of the adult, and on a wet-weight basis the protein concentration in the tissue shows a gradual increase throughout life; but the course of this change is not even, and there are fluctuations in the protein content corresponding to the morphological changes occurring in different parts of the brain as they become functionally active. The protein concentration is higher at first in the medulla and hypothalamus, which are also the first regions to mature: it increases later in the cerebral cortex and cerebellum, which are phylogenetically newer and the last to become functionally active.

The experiments in which the rate of incorporation of labelled amino-acids into isolated tissue was measured *in vitro* have been extended by measuring the rate of incorporation into the proteins of the brain *in vivo* of amino-acids introduced directly into the cerebrospinal fluid (Gaitonde and Richter, 1956). The rate of amino-acid incorporation is considerably higher in the newborn animal than in the adult, and there is a gradual falling off in the rate with increasing age (Chart).

The changes occurring during the growth and maturation of the brain include changes in the cell population of the tissue. In the earlier stages of development the brain tissue is made up largely of

immature nerve cells, and these are the first cells to appear in considerable numbers in the mature form. The neurones reach their maximum numbers relatively early (in the human species before birth), and they are soon outnumbered by the cells of other types, which eventually make up 90% or more of the total number present in the brain. With a composite tissue of this kind considerable changes with age are to be expected in the biochemical as well as in the morphological characteristics of the tissue. Changes in enzymic activity with age have been reported by a number of investigators, and Flexner (1951-2) has related the enzymic changes to the morphological changes occurring during maturation. He has shown that there are striking changes in enzymic activity at a "critical period" during which the nerve cells become functionally mature.

Many enzyme systems, such as those concerned in the synthesis of cholesterol, disappear with the cessation

The variation with age in the rate of incorporation of ^{35}S -methionine into the proteins of the rat brain.

of growth, and they are found to be absent or hardly detectable in the adult brain. This is true for certain enzymes related to the protein metabolism. Thus brain homogenates from the 1-day-old rat will incorporate ^{14}C from ^{14}C -labelled glucose into amino-acids, including essential amino-acids such as cystine, lysine, and histidine (Winzler *et al.*, 1952); but in homogenates from adult brain this property is missing, and the isotope is incorporated only into amino-acids such as glutamic and aspartic acids, which occupy a special position in view of their relation to the citric acid cycle.

*Lecture delivered at the Institute of Neurology, National Hospital, Queen Square, London, on October 6, 1958.

As development proceeds, successive changes in the activities of the individual enzymes take place. New enzymes appear, increase in activity, and later decline. The changes in metabolism may be considered in terms of ascending and descending curves of enzymic activity, which effect a gradual change from one metabolic pattern to another as the "metabolism of growth" is replaced by that of the mature cells in the functionally active centres of the brain. At first the brain functions mainly as a controlling centre in regulating the relatively slow and diffuse humoral mechanisms of the neuro-endocrine system. As the higher centres mature, the brain assumes other functions in which speed of action is of primary importance, and it becomes a centre for the rapid analysis of sensory data and the computation required for adaptive behaviour at the adult level. For this purpose it elaborates a system of neurones with large myelinated high-speed axons; and metabolism is therefore adapted to the synthesis of the special proteolipids and other complex substances needed for the laying down of myelin.

Effect of Environmental Factors on Protein Metabolism and Growth

The proteins of the brain are more resistant in general than those of other organs to depletion under conditions of starvation; but a severe protein deficiency in the mother can lead to the death or deformation of a foetus, and it is likely that a faulty environment is the cause of the changes that are seen, for example, in the small "ill-finished" brain of the mongol child. The effects of prolonged protein deficiency on the brain during the early formative years of life are indicated by the mental symptoms of apathy and deep depression that appear in kwashiorkor. Mental symptoms have also been produced experimentally by the deliberate omission of a single essential amino-acid, such as methionine or lysine, from the diet (Rose *et al.*, 1950): the symptoms of nervous irritability and fatigue quickly disappear if the missing amino-acid is restored to the diet, with or without the knowledge of the subject.

Protein formation is controlled by the growth hormone of the anterior hypophysis and it is influenced particularly by the levels of cortisone and thyroid hormone. Thyroid hormone has little effect on the metabolism of the adult brain, owing perhaps to the protective action of the blood-brain barrier in preventing the entry of the hormone into the brain; but it is needed for the functional maturation of the brain in the infant, and in the young developing animal it not only increases the rate of oxygen consumption but it also increases the overall protein content of the brain (Reiss *et al.*, 1956). The precise way in which the thyroid hormone acts is not yet clear, but it has recently been shown that the enzymes succinic dehydrogenase and cholinesterase fail to develop in the cerebral cortex if an adequate level of thyroid hormone is not present (Hamburgh and Flexner, 1957).

The normal development of the nerve cells appears to depend on their receiving a sufficient amount of physiological stimulation during growth. This has been shown very convincingly in some recent experiments of Brattgård (1952), in which he compared the retinal ganglion cells of the normal rabbit with those of animals born and reared in darkness. In animals kept for ten weeks in darkness the retinal neurones failed to develop, and the content of protein and ribonucleoprotein was considerably reduced (see Table I). These observations may be relevant to the condition of *amentia*

sensoripriva, in which mental retardation is found in children deprived of forms of sensory stimulation normal for their age.

TABLE I.—*Effect of Physiological Stimulation on Retinal Ganglion Cells of the Rabbit (Weight in 10^{-4} mg./ μ^2 . Brattgård, 1952)*

Treatment		Ribonucleoprotein	Proteins
Daylight 10 weeks		0.47	0.31
Darkness "		0.0	0.16

The conditions required for the optimal growth and development of the brain during the foetal and post-natal periods are not yet clearly understood, but it would appear that environmental factors affecting the protein metabolism may be concerned in the causation of some of the neurological conditions, such as certain forms of cerebral palsy, in which the neurones fail to develop normally.

Proteins of the Brain

What is the nature of the proteins that are normally present in the brain? The earlier investigators were able to separate only five or six proteins from brain tissue. These include albumin, globulin, phosphoprotein, and nucleoprotein, which could be extracted in aqueous solution, and the insoluble proteins collagen, reticulin, and "neurokeratin": but none of these proteins was obtained pure and only one, neurokeratin, could be regarded as in any way characteristic of nervous tissue. Neurokeratin was obtained mainly from the white matter of the brain by treatment with strong acid followed by prolonged digestion with proteolytic enzymes, but it does not have the amino-acid content typical of a true keratin, and the neurokeratin prepared in this way would appear to be an artifact derived mainly from the inositol-containing proteolipids through the action of the drastic reagents used in its preparation (LeBaron and Folch, 1956). It has recently been confirmed that the neurokeratin described by histologists as a structural component of the myelin sheath also has the properties of a proteolipid (Koenig, 1959). Collagen and elastin are present in significant amounts in the connective-tissue sheath of peripheral nerve, but in brain tissue they are present only in very small amounts (about 0.2% of the normal protein content), which suggests that they may be derived from the blood vessels and not from the neurones or glial cells.

Recent work has added greatly to the number of proteins known to be present in nervous tissue. Up to 10 proteins have now been separated by electrophoresis from the soluble cytoplasmic fraction of the brain proteins (Robertson, 1957), and the proteins of the cell nuclei, mitochondria, and microsomes, have been fractionated in various ways (Clouet and Richter, 1959; Robertson, 1959). By the use of milder methods of extraction it has been possible to isolate in various degrees of purity a liponucleoprotein (Folch and Uzman, 1948), three copper-containing proteins—cerebrocuprein I, II, and III (Porter and Folch, 1957)—three proteolipids (Folch and Lees, 1957), the physiologically active van Dyke protein of the hypophysis, and a number of different enzymes, including cholinesterase.

It used to be believed that tissues such as brain were made up largely of structural proteins and that the quantity of enzymes present was relatively small; but it has become increasingly hard to draw a distinction between the proteins with enzymic activity and those with a structural role. Besides the enzymes in the soluble phase, certain enzymes are now known to be closely associated with structures such as the mito-

chondrial membranes, with the microsomes, and even with the myelin sheath (Schmitt, 1957). There is reason to believe that, as in muscle and other tissues, enzymes may make up the main bulk of the proteins in the cells of the living brain. The number of enzymes hitherto identified in nervous tissues runs into a considerable figure, but it is likely to form only a small fraction of the total number that are present, and if every enzyme is regarded as a separate protein entity the total number of proteins must be very large. Estimates based on the number of genes in the organism, assuming the presence of one enzyme for every gene, lead to figures of the order of more than 20,000 for man.

The proteins of the brain are not the same as those in peripheral nerve, and the protein distribution varies in different parts of the brain. This is shown by studies of the distribution of enzymes, some of which are present in higher concentration in the grey matter than in the white. Differences have also been shown in the proteins in different topographical regions. Thus the enzyme cholinesterase is present in relatively high concentration in the caudate nucleus. Differences have been found again in the distribution of the soluble proteins separated by electrophoretic methods: the proteins in the cerebral cortex differ significantly from those in the hypothalamus and other regions of the brain (Robertson, 1959).

Protein Changes in Pathological Conditions

Gross changes in protein structure are recognized in many "organic" conditions, and they are shown very well by the classical histological staining techniques, which are mainly designed for demonstrating proteins. These methods have also led to the recognition of protein changes of a milder kind associated with less drastic forms of injury to the nerve cells. Of particular interest are the characteristic changes known as "chromatolysis," in which there is a dissolution of the liponucleoprotein aggregates constituting the Nissl granules in fixed preparations. This is not a simple proteolysis, for the proteolytic enzymes of nervous tissues do not act directly on nucleoproteins. There is evidence that the dissolution of the Nissl granules during chromatolysis is due to the action of a ribonuclease which first splits up the large ribonucleic acid residues (Gersh and Bodian, 1943). Other concomitant changes, such as the swelling of the nerve cell bodies and dilution of the cell contents, are attributable to the increase in osmotic pressure in the cytoplasm due to the liberation of smaller nucleotide molecules and protein fragments as proteolysis ensues. Chromatolysis is an unspecific reaction of the nerve cell to an injury of any kind, and it is seen in many different pathological conditions. In the recovery process there is an active synthesis of new protein in the nerve cell bodies, and protein passes out into the axoplasm.

Very little is known about the distribution of soluble proteins in the brain in pathological conditions, but preliminary investigations by electrophoretic methods have shown that there is an abnormal distribution, with a relative increase in the slow-moving " γ -globulin" fraction in the brains of patients with subacute sclerosing leucoencephalitis (Karcher *et al.*, 1959). Electrophoretic studies of the proteins present in oedematous areas of the brain have shown a relative increase in the fast-moving albumin and α -globulin fractions: this has been found, for example, in the oedematous areas adjacent to cerebral tumours and other lesions of the brain. It is known that the

proportion of fast-moving proteins is higher in the immature infant brain than in the adult, and it has been reported that they are also present in abnormal amounts in patients suffering from certain forms of epilepsy (Kiyota, 1957). It has been suggested by Kiyota (1957) that these fast-moving proteins are highly hydrophilic and so may account for the higher water content and the greater tendency to cerebral oedema, and hence to convulsions in infants and in epileptics. The proteins of the infant brain contain a higher arginine/histidine ratio than those of the adult, and in this connexion it may be relevant that an abnormally high arginine/histidine ratio has been found in the proteins of the brain of a patient suffering from late amaurotic familial idiocy (Block, 1937). The presence of an abnormal form of copper protein has been reported in the brains of patients with Wilson's disease (Porter, 1959).

Brain tissue contains a powerful cathepsin which is about 12 times more active than that in muscle. This enzyme may be expected to act as a transpeptidase under normal physiological conditions, but it may act as a proteolytic enzyme and cause the breakdown of proteins under pathological conditions. Brain tissue also contains a "neutral proteinase" which can break down proteins at the neutral pH (Ansell and Richter, 1954). It has recently been reported that this enzyme, or a similar proteolytic enzyme, is released from the brain into the cerebrospinal fluid in patients suffering from migraine and other active neurological conditions (Chapman and Wolff, 1958). Chapman and Wolff (1958) have suggested that the polypeptides formed through the action of this enzyme may play a part in stimulating the pain nerve endings and in causing the vascular changes associated with attacks of migraine.

In view of the large number of enzymes that are believed to be present, the scope for individual variation in enzymic activity is clearly very great, and it is hardly surprising if it occasionally happens that, for genetic or other reasons, a particular enzyme is missing or deficient in the cell. A number of pathological conditions are now recognized in which the metabolism of the brain is affected by metabolic errors of this kind. They include such well-known examples as phenylketonuria, in which there is a congenital inability to hydroxylate phenylalanine, and the congenital lipidoses or "storage" diseases. An abnormal distribution of enzymes in the brain has been reported in patients suffering from vascular disorders of the brain, and it has been suggested that a faulty distribution or imbalance of enzymes might account for some of the changes occurring in psychotic conditions (Richter, 1957).

Protein Metabolism of the Adult Brain

Analyses of the blood entering and leaving the brain have shown that there is an active utilization of glucose, but practically no utilization of the amino-acids in the blood traversing the brain. There is also very little uptake of labelled amino-acids such as ^{14}C -tyrosine *in vivo* by the brain. These observations led to the view that the proteins of the brain are metabolically inactive; but more recent work has shown that the low uptake of labelled amino-acids into the brain is largely attributable to the blood-brain barrier, and there is an active incorporation of amino-acids if the blood-brain barrier is bypassed by introducing them direct into the cerebrospinal fluid (Gaitonde and Richter, 1956). Calculations of the mean half-life of the proteins during a period of 20–60 minutes' incorporation of ^{35}S -

methionine indicated a mean half-life of 14 days. Since it is known that the proteins of the brain are not homogenous it is clear that some of the proteins will have a longer and others a shorter half-life, but the estimate of 14 days may be compared with other estimates of 6 days for the proteins of the visceral organs and up to 50 days for the carcass proteins of the rat. Figures ranging from 6.2 to 15.2 (mean 10.7) days have recently been reported for the half-life of the mixed protein of the mouse brain determined for a similar period by means of ^{14}C -lysine (Waelsch, 1957). Such estimates for mixed proteins tell us nothing about the rates of incorporation into individual protein fractions, and they are also subject to error, since they assume a uniform amino-acid "pool" in the brain and ignore the fact that the specific activity of the amino-acids must differ in the different cell compartments in the brain.

More recent measurements of the rate of uptake of labelled amino-acids into isolated cell particles obtained from brain tissue by differential centrifugation have shown a relatively high rate of incorporation in the proteins of the microsomes, while the uptake into the proteins of the cell nuclei, mitochondria, and supernatant fraction is relatively slow (Clouet and Richter, 1959). The protein showing the highest rate of incorporation is a liponucleoprotein corresponding to the Nissl granules: it can be extracted from the microsomes by means of dilute alkali, and contains approximately equal amounts of lipid and protein and 3.8 g. nucleic acid per 100 g. of protein. Estimates of the half-life of this liponucleoprotein based on the rate of incorporation of ^{35}S -methionine and on the shape of the specific activity-time curve have given figures of the order of 50–100 minutes for the half-life of this protein (Clouet and Richter, 1959). The proteins of the nuclei, mitochondria, and soluble fractions give considerably longer half-lives: the rate of incorporation of amino-acids into the white matter of the brain, and into the proteolipids, which are a major constituent of the white matter, is relatively slow.

The rate of incorporation of amino-acids varies in different parts of the brain. This has been shown in experiments by an autoradiographic method in which the distribution of radioactivity in the tissue was studied after administering ^{35}S -methionine to animals *in vivo* by the intracisternal and intraperitoneal routes (Cohn *et al.*, 1954). It was found that the uptake of ^{35}S -methionine was considerably greater in the grey matter than in the white matter of the brain. In the brains of 1-day-old rats the incorporation was relatively diffuse, but was more pronounced in the cerebral cortex than in the regions mainly containing nerve fibres. In older animals the incorporation was most active in the cellular layers containing a high proportion of nerve cell bodies. There was a marked incorporation in the cerebellum, in the cerebral cortex, and in the *pyramidalis* layer of Ammon's horn. The highest rate of incorporation was in the supraoptic nucleus and other hypothalamic nuclei containing neurosecretory cells. These observations have been confirmed by direct measurements of the radioactivity of regions of the brain removed by dissection after the administration of a labelled amino-acid (Cohn *et al.*, 1959).

The rate of amino-acid incorporation *in vivo* is decreased in narcosis with sodium pentobarbitone or ether, and there is a marked decrease if the temperature is allowed to fall. There is also a decrease of about

25% in the amino-acid incorporation during insulin coma, but electrical stimulation of the brain does not greatly affect the amino-acid incorporation.

TABLE II.—*Amino-acid Turnover of Proteins of the Rat Brain in vivo after administering ^{35}S -methionine by Intracisternal Injection (Gaitonde and Richter, 1956)*

	Specific Activity Ratio	Change %	P
Normal	99	—	—
Ether	65	—34	0.02
Pentobarbitone	75	—24	0.001
Reduced temp.	29	—70	0.001
Insulin hypoglyc.	75	—24	0.003
Stimulation	80	—19	0.001

Besides the incorporation of amino-acids there are a number of other reactions in which the proteins of the brain are known to take part. It has recently been shown that there is a reversible uptake and release of ammonia from the amide groups of the glutamine residues in the brain proteins (Vrba, 1956). This reaction is of particular interest, since there is evidence that functional activity is associated with the liberation of free ammonia in the brain, and it has been shown that changes can be produced in the amide nitrogen content of the brain proteins of the rat during prolonged neuromuscular activity. The tissue proteins have also been shown to combine with various pharmacologically active amines, and the uptake has been measured by the use of the labelled metabolites ^{14}C -mescaline and ^{14}C - β -phenylethylamine (Block, 1954; Clarke *et al.*, 1957).

Further evidence of the metabolic activity of the proteins of the brain *in vivo* has been obtained in studies of the uptake of labelled phosphate into a phosphoprotein that is present in the brain. It has been shown that the phosphate in these phosphoproteins is combined in the hydroxyl groups of the serine units: the rate of turnover is influenced by a number of factors including electrical stimulation of the tissue (Heald, 1958). Evidence has been obtained that electrical stimulation of the brain under certain conditions can cause a reversible change in the configuration of the protein molecules, which is probably attributable to a partial hydrolysis of amide bonds (Ungar *et al.*, 1957).

The reason for the active protein metabolism in the brain has been a subject for considerable speculation. It is known that under special conditions, where there is a deficiency of glucose, the brain is able to utilize protein as an alternative source of energy, and recent work has suggested that the metabolism of functionally active neurones differs from the resting metabolism in

TABLE III.—*Utilization of Substrates by Stimulated Nerve (Mullins, 1953)*

Increase % in CO_2 over Resting Metabolism		Increase % in CO_2 over Resting Metabolism	
Glucose	—22	Glycine	50
Acetate	—51	Alanine	80
Pyruvate	0	Glutamate	140
Lactate	0		

that there is a preferential utilization of amino-acids. Thus, stimulated nerve differs from resting nerve in showing a preferential utilization of glycine, alanine, and glutamic acid (Mullins, 1953) (Table III). The active synthesis of protein in the neurosecretory cells of the hypothalamus is now well established, and these observations suggest that there may be an active utilization of protein associated with functional activity in other parts of the brain.

REFERENCES

- Ansell, G. B., and Richter, D. (1954). *Biochim. biophys. Acta*, **13**, 87, 92.
- Block, R. J. (1937). *J. biol. Chem.*, **120**, 467.
- Block, W. (1954). *Hoppe-Seyler's Z. physiol. Chem.*, **296**, 108.
- Brattgård, S. O. (1952). *Acta radiol (Stockh.)*, Suppl. 96.
- Chapman, L. F., and Wolff, H. G. (1958). *Trans. Ass. Amer. Physns.*, **71**, 210.
- Clarke, D. D., Neidle, A., Sarkar, N. K., and Waelsch, H. (1957). *Arch. Biochem.*, **71**, 277.
- Clouet, D. H., and Richter, D. (1959). *J. Neurochem.*, **3**, 219.
- Cohn, P., Gaitonde, M. K., and Richter, D. (1954). *J. Physiol.*, **126**, 7 P.
- (1959). *J. Neurochem.*, in press.
- Flexner, L. B. (1951-2). *Harvey Lectures*, **47**, 156.
- Folch, J., and Lees, M. (1957). *J. biol. Chem.*, **191**, 807.
- and Uzman, L. L. (1948). *Fed. Proc.*, **7**, 155.
- Gaitonde, M. K., and Richter, D. (1956). *Proc. roy. Soc. (B)*, **145**, 83.
- Gersh, I., and Bodian, D. (1943). *J. cell. comp. Physiol.*, **21**, 253.
- Greenberg, D. M., Friedberg, F., Schulman, M. P., and Winnick, T. (1948). *Cold Spring Harbor Symp. quant. Biol.*, **13**, 113.
- Hamburgh, M., and Flexner, L. B. (1957). *J. Neurochem.*, **1**, 279.
- Heald, P. J. (1958). *Biochem. J.*, **68**, 580.
- Karcher, D., van Sande, M., and Lowenthal, A. (1959). *J. Neurochem.*, **4**, in press.
- Kiyota, K. (1957). *Ibid.*, **1**, 301.
- Koenig, H. (1959). *Ibid.*, **4**, in press.
- LeBaron, F. N. and Folch, J. (1956). *Ibid.*, **1**, 101.
- Mullins, L. J. (1953). *Amer. J. Physiol.*, **175**, 358.
- Porter, H. (1959). In *Chemical Pathology of the Brain*, edited by J. Folch. Pergamon Press, London. In press.
- and Folch, J. (1957). *J. Neurochem.*, **1**, 260.
- Reiss, J. M., Reiss, M., and Wyatt, A. (1956). *Proc. Soc. exp. Biol. N.Y.*, **93**, 19.
- Richter, D. (1957). *Schizophrenia: Somatic Aspects*. Pergamon Press, London.
- Robertson, D. M. (1957). *J. Neurochem.*, **1**, 358.
- (1959). *Ibid.* In press.
- Rose, W. C., Johnson, J. E., and Haines, W. J. (1950). *J. biol. Chem.*, **182**, 541.
- Schmitt, F. O. (1957). In *Metabolism of the Nervous System*, edited by D. Richter. Pergamon Press, London.
- Ungar, G., Aschheim, E., Psychoyos, S., and Romano, D. V. (1957). *J. gen. Physiol.*, **40**, 635.
- Vrba, R. (1956). *J. Neurochem.*, **1**, 12.
- Waelsch, H. (1957). In *Metabolism of the Nervous System*, edited by D. Richter, p. 431. Pergamon Press, London.
- Winzler, R. J., Moldave, K., Rafelson, M. E., and Pearson, H. E. (1952). *J. biol. Chem.*, **199**, 485.

TRIAMCINOLONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

MALCOLM THOMPSON, M.D., M.R.C.P.

Consultant Physician, Department of Physical Medicine,
Royal Victoria Infirmary, Newcastle upon Tyne

Triamcinolone is a synthetic steroid, being the 9 α -fluoro-16 α -hydroxy analogue of prednisolone (see Formula). It has been shown to possess powerful anti-inflammatory properties with minimal mineralo-corticoid activity. Bernstein *et al.* (1956) reported that, by rat-liver glycogen assay, triamcinolone was 18 to 36 times as potent as hydrocortisone, and in the adrenalectomized rat it did not produce any sodium retention. Hellman *et al.* (1957) described its clinical and metabolic effects, and demonstrated that it had excellent anti-inflammatory properties with, in ordinary therapeutic dosage, little or no effect upon nitrogen, calcium, potassium, or sodium balance. Assessment of the anti-inflammatory effects of triamcinolone suggested that it was more powerful than prednisolone in an approximate ratio of 4:3 when administered orally.

Sherwood and Cooke (1957) described the results of treatment of 26 patients suffering from allergic conditions, chiefly asthma or dermatitis, and thought that an equal weight of triamcinolone was about twice as potent as prednisone or prednisolone. Rein *et al.*

(1957) also reported upon the use of triamcinolone in dermatological cases, and concluded that an equivalent therapeutic effect was produced by a dosage between one-half and two-thirds of that of prednisolone. Shelley *et al.* (1958) considered that triamcinolone had a significant suppressive effect on psoriasis in 60% of their 60 cases, but that the relapse which invariably followed cessation of treatment limited its value.

Hartung (1958) reported favourably on the use of triamcinolone in 67 patients suffering from rheumatoid arthritis, and stated that it possessed several advantages over other steroids, including fewer gastro-intestinal symptoms. Dubois (1958) treated 31 cases of disseminated lupus erythematosus with triamcinolone, and his experience suggested that this new steroid did not precipitate gastro-duodenal symptoms or lesions. Hart *et al.* (1958) did not find any evidence that triamcinolone either aggravated or reduced gastro-duodenal side-effects in their series of 25 rheumatoid patients, all of whom had received previous treatment with prednisolone.

Since the demonstration by Bunim *et al.* (1955) that the Δ -1- or predni- analogues possessed four or five times the anti-inflammatory activity of cortisone and hydrocortisone, with much fewer sodium-retaining effects, there have been further attempts to find even more powerful steroid compounds. The mere anti-inflammatory potency of a steroid compound is not, of itself, important in assessing the value of the drug as a therapeutic agent, as a less potent steroid could be administered in larger dosage provided this did not produce undesirable side-effects. It is largely on the basis of side-effects, therefore, that a new steroid is to be evaluated. The lessening or elimination of mineralo-corticoid effects, especially hypertension and hypopotaemia, are important considerations, but other side-effects to be considered are peptic ulceration, mental disturbance, osteoporosis, lowered glucose tolerance, purpura, telangiectasia, and subcutaneous haemorrhages, facial mooning and flushing, and acne and hirsuties.

The purposes of the present investigation were to determine (a) whether triamcinolone was as effective or better than prednisolone when administered in a dosage not exceeding four-fifths of the prednisolone dosage; (b) whether triamcinolone warranted a place for selected, or indeed all, patients for whom systemic