assumed the chairmanship; they were repeated recently when a minister warned that if the system failed "it could not be imagined that nothing would be put in its place." This was when the various expressions of concern to which I referred early in this lecture were mounting.

A regime with bite?

If a coercive regime is to be established it will have to carry heavy penalties for breaching the code if it is to have bite. This must change the character and procedures of the Press Council. There would have to be formal procedures, with entitlement to legal representation and with provision for appeal. The currently constituted Press Council of part time volunteers is not the body to undertake those tasks. This may simply argue for change in the constitution of the council, and it is not in itself a decisive objection. What is of fundamental importance is that a coercive procedure, with heavy penalties, would change the whole conception of the council. At present its reach extends far beyond the law; the imposition of penalties for breach of its principles turns those principles effectively into rules of law which are rules made not by parliament, not by common law courts, but by the Press Council itself. Is this understood? Is it realised that what will be imposed is a regime of press law? And is it to reach beyond financial penalty into suspension of a paper or a journalist? Are we to come back to the notion of a licensed press in this way?

I would, however, carefully explore the desirability of expanding the reach of the law. Specifically, I believe that we need to explore the case for statutory protection of privacy against media intrusion, and I

have done so for many years. There is no more and no less difficulty and uncertainty in an adjudication by judicial decision than by the Press Council; the principles are set out in Press Council rulings, and the Press Council declarations of principle are those that the courts would apply. The only difference lies in the sanction, and if, as is shown, the media or sections of it will not comply with the existing regime one with penalty attached is sensibly to be put in its place. Likewise, in the context of the responsibility to report accurately we have to look seriously at properly devised and court controlled legislation for the right of reply. The essence of the matter is that the reply must be court controlled, and a procedure should be devised that is expeditious, simple, and inexpensive.

Indeed, the issues entailed in right of reply are more important, though less spectacular, because inaccuracy in reporting fact is pervasive; no section of the press is free of it. And if offending papers will not comply voluntarily, expeditiously, and adequately with a demand for reasonable correction of inaccurate report or fact other means of assuring it must be investigated. Only a short time ago Brian MacArthur wrote in the *Sunday Times* that "newspapers which needlessly haggle over corrections—a few journalists in my experience will readily admit to error . . . will have only themselves to blame" for right of reply legislation. Just so; in my view there is a powerful case for the enactment of such a law.

So I believe that serious consideration should be given to expanding the regime of the law in these two areas. As in the existing case of defamation, a person may in either case elect to go to the Press Council rather than to the courts for a remedy; the courts should, however, be available to him.

Lesson of the week

Effects of immunoscintigraphy with monoclonal antibodies in assays of hormones and tumour markers

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In 1975 Kohler and Milstein first produced monoclonal antibodies in vitro by fusing B lymphocytes producing antibody from an immunised mouse with cells derived from an immortal B lymphocyte tumour.¹ Since then the use of monoclonal antibodies has had an important impact in medicine and clinical chemistry, both in vivo and in vitro. We present a clinical problem inherent in the use of monoclonal antibodies in vivo illustrated by a case history.

Methods

Immunometric assays were used to measure the following: thyroid stimulating hormone (Riagnost; Behringwerke, West Germany); carcinoembryonic antigen (Enzym-Test; Boehringer Mannheim, West Germany); prostatic acid phosphatase (PAP-EIA diagnostic kit; Abbott, North Chicago, United States); α fetoprotein (Riabeal; Abbott, North Chicago); and prostate specific antigen (Tandem-PSA; Hybritech, Luik, Belgium). For these assays monoclonal antibodies are bound to a solid phase and incubated with serum samples to bind the specific antigen; "sandwiches" are formed with a second monoclonal antibody that is directed against this antigen.²

Calcitonin was measured with a non-commercial assay with polyvalent goat serum (Dr G H Hackeng, Bergweg Hospital, Rotterdam.) Scintigraphy was performed with radiolabelled anti-carcinoembryonic antigen monoclonal antibody (Imacis-1; International Cis, Saint Quentin, France). Human antibodies against mouse antibodies were detected with an enzyme linked immunosorbent assay (ELISA). After the solid phase was coated with an OKT3 mouse monoclonal antibody (Ortho Pharmaceutical Corporation, New Jersey, United States) the serum samples were added. After incubation the unbound material was removed by washing. Goat antibody labelled with alkaline phosphatase (Southern Biotechnology Associates, Alabama, United States) was added to the bound antibodies (IgG and IgM) and the results visualised at 405 nm.

Case history and discussion

In January 1988 a 61 year old man with a seven year history of tumours at various sites was admitted because of progressive growth of a tumour in his neck. He was taking replacement thyroxine, and there were clinical signs of thyrotoxicosis. The results of routine laboratory urine and blood tests were normal. Plasma

Doctors should inform laboratories when patients have been given animal monoclonal antibodies so that misleading results are prevented

concentrations of calcitonin and carcinoembryonic antigen (tumour markers for medullary thyroid carcinoma) were raised at 31 000 ng/l (normal <140 ng/l) and 245 µg/l (normal <5 µg/l), respectively. His prostatic acid phosphatase concentration was repeatedly raised at >230 µg/l (normal <5 µg/l). Six months before he was admitted his prostatic acid phosphatase concentration had been 10 µg/l. α Feto-protein, determined because of an area of lower density in the liver detected by computed tomography, was also raised at 80 U/l (normal <20 U/l). Thyroid function tests showed biochemical signs of thyrotoxicosis. His total thyroxine concentration was increased at 240 nmol/l (normal about 145 nmol/l during thyroxine supplementation), as was his thyroid stimulating hormone concentration at 36.5 mU/l (normal <2 mU/l during supplementation). Three months before he was admitted his thyroxine replacement dose had been increased by 50 µg to 175 µg daily. At a dose of 125 µg his concentration of thyroid stimulating hormone had been 12.9 mU/l, and it had further increased during treatment with 175 µg thyroxine.

Cytological aspiration of the tumour in his neck showed a relapse of a previous medullary carcinoma. A prostatic carcinoma with metastases was also suspected because of the raised prostatic acid phosphatase concentration, though it was not evident on physical examination or computed tomography. As the concentration of prostate specific antigen was also greatly increased (715 µg/l, normal 0-10 µg/l) we considered it unlikely that the medullary carcinoma had produced prostatic acid phosphatase. The cause for the increased thyroid stimulating hormone concentration was also

FIG 1—Results of assay of thyroid stimulating hormone concentration showing apparent plateau at sample of 50 µl serum, thus explaining abundance of antigen in sample

Results of immunometric assays before and after addition of mouse serum to bind tumour antimouse antibody in patient reported on here (case 1) and three other patients

Case No	Date of assay	Thyroid stimulating hormone (mU/l)		α Fetoprotein (µg/l)		Prostatic acid phosphatase (µg/l)		Carcinoembryonic antigen (µg/l)	
		Before	After	Before	After	Before	After	Before	After
1*	12 May 1986	15.7	8.72	13	6	11.4	5.7	38.4	4.6
	19 Feb 1988	26.0	0.14	74	6	94.0	3.7	335.0	5.3
	23 Feb 1988	30.6	0.31					389.0	4.7
2†	23 Sept 1986			3				174.0	
	14 Jan 1987			3				678.0	
	25 Feb 1987	8.24	0.45	10	3	28.6	5.0	1712.0	1106.0
3‡	26 Oct 1987	0.08	0.08	3	3	3.3	1.1	2690.0	2585.0
	26 Feb 1988	0.27	0.24	3	3				
4§	22 Feb 1988	0.38	0.59						

*Not fully supplemented with thyroxine at 12 May 1986. First anticarcinoembryonic antigen scintigraphy 17 October 1985, second 9 April 1987.

†Carcinoma of unknown origin. First anticarcinoembryonic antigen scintigraphy 25 September 1986, second 5 February 1987.

‡Medullary thyroid carcinoma with metastases. Anticarcinoembryonic antigen scintigraphy 24 October 1985.

§Medullary thyroid carcinoma with metastases. Anticarcinoembryonic antigen scintigraphy 6 January 1987.

FIG 2—Serum concentrations of thyroid stimulating hormone and calcitonin (top) and carcinoembryonic antigen and prostatic acid phosphatase (bottom) over time. Arrows show when diagnostic scintigraphy with anticarcinoembryonic antigen (mouse) monoclonal antibody was performed

not clarified as a pituitary tumour producing this hormone was excluded by computed tomography. The cause of the raised α fetoprotein concentration was also obscure. Medullary carcinoma of the thyroid does not produce α fetoprotein, and there was no evidence of a testicular tumour or other tumours with embryonic elements.

The explanation for all these raised tumour markers was established after the thyroid stimulating hormone concentration was assayed at different dilutions of the serum (fig 1). At a volume of 50 µl serum or more there seemed to be a threshold for binding of antigen (thyroid stimulating hormone) and antibody (mouse monoclonal antibody against thyroid stimulating hormone). Usually thyroid stimulating hormone concentration is assayed in a sample of 200 µl serum. This result suggests a plateau of antibody binding of thyroid stimulating hormone and so explains the abundance of antigen (thyroid stimulating hormone) in the assayed sample. The definitive explanation was found in the course of the serum concentrations of thyroid stimulating hormone, prostatic acid phosphatase, calcitonin, and carcinoembryonic antigen before this admission. Figure 2 shows that the concentrations of thyroid stimulating hormone and calcitonin increased at the end of 1986 and rose sharply in May 1987. Moreover, the carcinoembryonic antigen and the prostatic acid phosphatase concentrations increased from March 1987. In November 1985 and April 1987 our patient had been injected with a mouse monoclonal anticarcinoembryonic antigen antibody to detect metastases of the medullary carcinoma by scintigraphy. Mouse monoclonal antibodies had also been used to assay thyroid stimulating hormone, carcinoembryonic antigen, prostatic acid phosphatase, and α fetoprotein concentrations.

The explanation of our findings was that the patient had produced human antimouse antibodies after he had undergone the first scintigraphy in November 1985. The second scan in April 1987 boosted the production of these antibodies. The diagnostic monoclonal antibodies used in the in vitro assays were also bound by human antimouse antibodies (fig 3), thereby causing falsely high results. This interference could have been prevented by adding mouse serum to the human serum before its assay (fig 3). Thus

FIG 3—Mechanism by which human antimouse antibodies induce falsely increased thyroid stimulating hormone concentrations in immunoradiometric assay. Interference can be inhibited by adding mouse serum before starting the assay

A—Thyroid stimulating hormone in serum of patients reacts with monoclonal (mouse) antibody (1) against thyroid stimulating hormone. This monoclonal antibody is bound to solid phase. Second antithyroid stimulating hormone mouse monoclonal antibody labelled with iodine-125 (2) is added. After binding to thyroid stimulating hormone a radiolabelled sandwich is formed. Unbound materials present in specimen are removed by washing

B—Human mouse antibodies (3) bind to both monoclonal mouse antibodies (1, 2) forming a sandwich which imitates sandwiches formed by thyroid stimulating hormone

C—Mouse immunoglobulins (4) are added to human mouse antibodies (3) before start of assay. In this way generation of sandwiches imitating "thyroid stimulating hormone sandwiches" is prevented because unlabelled sandwiches are formed, which do not disturb the assay

prostatic acid phosphatase, carcinoembryonic antigen, thyroid stimulating hormone, and α fetoprotein concentrations were all falsely raised (table, case 1). The calcitonin concentration, assayed by polyvalent goat serum, was not falsely raised (data not shown), and its increase was the real consequence of the growth of the medullary carcinoma of the thyroid.

The IgG antibody titre against mouse antibody measured in this patient by ELISA was 13.3 (normal value 8.9 (SD 2.0) (n=21)). He had the same titre of IgM antibodies against mouse antibodies as did a control group.

The table shows the results of assays in three other patients. One (case 2) also underwent diagnostic scintigraphy twice with anticarcinoembryonic antigen mouse monoclonal antibody and had falsely increased

results of assays. In cases 3 and 4 diagnostic scintigraphy was performed only once and the results of the laboratory assays were normal. The occurrence of human antimouse antibodies seems to be triggered specifically by a second scintigram.

Conclusion

Although monoclonal antibodies have a high degree of specificity, the animal source of these antibodies may cause problems. Repeated administration of animal monoclonal antibodies in humans can induce the formation of human antimouse antibodies, as shown in our patient. The amount of human antimouse antibodies produced seems to be related to the frequency of administration. These human antimouse antibodies can interfere with in vitro immunoassays that use an antibody of the same animal origin. This may lead to falsely high assay results. Such results can be circumvented by adding animal serum to the human serum before the assay. Falsely low values of immunoassays after in vivo use of animal monoclonal antibodies³ and the generation of human antibodies after the use of rabbit,⁴ goat,⁵ and bovine⁶ immunoglobulins have also been reported. Handling of animals and animal products also generates human antibodies that interfere in immunoassays.⁷

Doctors should be aware of the phenomenon because the results of these assays are often used as a basis for major diagnostic and therapeutic decisions.

We thank Dr C J Hesse for measuring IgG and IgM antibody titres and Joke M Nijse for secretarial help.

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ANY QUESTIONS

The dangers of aflatoxins impregnating nuts have recently been highlighted. Is it possible to eradicate this contamination in the home by heating nuts in an ordinary oven or a microwave oven, and if so how should it be carried out?

It is not possible to remove the aflatoxins in this way. Two processes have been proposed for degrading the aflatoxins, but neither of these is appropriate for use domestically.¹ The efficiency and safety of these processes are still topics for research, and the efficiency of the treatment would, in any event, need to be monitored. At present, therefore, the proper course of action is to avoid the consumption of contaminated nuts, and there is an advisory upper limit for total aflatoxins for nuts and nut products (10 μ g/kg) intended for human consumption. It is thus important to ensure that any nuts purchased are intended for human consumption. — D A T SOUTHGATE, head, *Agricultural and Food Research Council Institute of Food Research, Norwich*

1 Ministry of Agriculture, Fisheries, and Food. *Mycotoxins*. London: HMSO, 1987. (Food surveillance paper No 18.)